Small GTPases 4:1, 28–33; January/February/March 2013; © 2013 Landes Bioscience

# The secretory pathway in control of endoplasmic reticulum homeostasis

Nikoleta G. Tsvetanova
Department of Psychiatry; University of California at San Francisco; San Francisco, CA USA

**In eukaryotic cells, proteins and membranes are transported between successive compartments by vesicle trafficking. Since precise protein localization is crucial for a range of cellular functions, it is not surprising that vesicle trafficking plays a role in many processes, including cell division, signaling, development and even gene expression. We recently found evidence that the yeast secretory pathway directly regulates the dynamics of a key cell survival process, the unfolded protein response (UPR). UPR activation requires the processing of the transcription factor encoding RNA *HAC1*. We showed that the small yeast GTPase Ypt1, which regulates endoplasmic reticulum-to-Golgi trafficking, associates with and controls the RNA stability of unspliced *HAC1* under normal growth conditions. Other small GTPases of the Ypt family also interacted with the unprocessed RNA. Here, we speculate about the possible mechanism behind this novel secretory pathway-dependent regulation of endoplasmic reticulum homeostasis.**

**Keywords:** vesicle trafficking, Ypts, UPR, *HAC1* RNA, RNA degradation

Submitted: 09/04/12

Revised: 10/15/12

Accepted: 10/19/12

http://dx.doi.org/10.4161/sgtp.22599

Correspondence to: Nikoleta G. Tsvetanova; Email: nikoleta.tsvetanova@ucsf.edu

Commentary to: Tsvetanova NG, Riordan DP, Brown PO. The yeast Rab GTPase Ypt1 modulates unfolded protein response dynamics by regulating the stability of HAC1 RNA. PLoS Genet 2012; 8:e100286; PMID:22844259; http://dx.doi.org/10.1371/journal.pgen.1002862

## Introduction

In eukaryotes, *ras* family GTPases regulate the transport of proteins and membranes in and out of the cell. In the simplest eukaryote, the budding yeast *Saccharomyces cerevisiae,* these GTPases are called Ypts (yeast protein transport). They are involved in different aspects of intracellular membrane trafficking, including vesicle formation, motility, docking, and membrane fusion and remodeling. There are 11 Ypts, and each of them plays compartment-specific roles in endocytosis (Ypt7, 51/52/53) or exocytosis (Ypt1, Ypt32/32, Sec4). GDP-bound inactive Ypts are found in complex with GDI (GDP-dissociation inhibitor) in the cytosol, and the nucleotide exchange occurs after recruitment to the appropriate membrane. Although we still lack knowledge of a universal mechanism for Ypt targeting to membranes, in vitro assays in mammalian cells showed that a GDI-GTPase complex carries all the information necessary for proper GTPase delivery to the target membrane.[1,2] Further, evidence from domain swap experiments suggests that the Ypt C-terminal prenylated domains called hypervariable domains, which associate with GDI,[3] can act as localization tags.[4,5] These hypervariable domains may also participate in the interactions of Ypts with GDFs (GDI displacement factors),[6] the proteins that displace GDI and facilitate the association of Ypts with the target membrane. Since GDFs localize to different compartments, they are likely to provide an additional level of specificity for GTPase targeting (for extensive reviews on GTPase targeting to distinct membranes, see refs. 6–8). Once on a membrane, Ypts undergo a conformational "on" change when stimulated by GEFs (guanine nucleotide exchange factors), and can interact with downstream effector proteins to regulate trafficking. Conversely, when GAPs (GTPase activating proteins) associate with the GTPases, they turn them "off." As protein transport is crucial for all cellular processes, it is not surprising that vesicle trafficking is coordinated with other processes. Here we discuss novel findings which link protein transport and a key eukaryotic stress survival response, the unfolded protein response (UPR).

**Table 1.** Secretory pathway components shown to associate with RNAs

| Protein name | Annotated function* | Annotated localization* |
|---|---|---|
| Sec1[#] | Docking and fusion of exocytic vesicles | Bud neck; bud tip |
| Sec16[#] | COPII vesicle coat component; transport of ER vesicles | COPII vesicle |
| Sec31[#] | COPII vesicle coat component; transport of ER vesicles | COPII vesicle |
| Sec26[#] | COPI vesicle coat component; ER-to-Golgi transport | COPI vesicle |
| Sec27[#] | COPI vesicle coat component; ER-to-Golgi transport | COPI vesicle |
| Ubp3[#] | Ubiquitin-specific protease; ER-Golgi anterograde and retrograde transport | Cytosol |
| Vtc1[#] | Subunit of the vacuolar transporter chaperone (VTC) complex involved in membrane trafficking | Vacuole; ER |
| Ypt1[#,‡] | Rab family GTPase; ER-to-Golgi step of the secretory pathway | ER and Golgi |
| Ypt7[‡] | Rab family GTPase; late endosome-to-vacuole sorting | Vacuole |
| Ypt32[‡] | Rab family GTPase; trans-Golgi-to-plasma membrane sorting | Endosome and Golgi |
| Rho3[‡] | Rho/Rac GTPase; establishment of cell polarity | Cytosol; cell bud; plasma membrane |

*Data from the Saccharomyces genome database (www.yeastgenome.org); [#]Data from Tsvetanova NG, Klass DM, Salzman J and Brown PO (2010); associated with total mRNA; [‡]Data from Tsvetanova NG, Riordan DP and Brown PO (2012); associated with *HAC1* RNA.

## Crosstalk between Vesicle Trafficking and Other Cellular Processes

We will start by summarizing examples of crosstalk between the secretory pathway and other processes with special emphasis on the interplay between membrane transport and RNA regulation. Systematic deletion screens performed in *Saccharomyces cerevisiae* have shown a role for vacuolar protein sorting genes (*VPS*) in the regulation of telomere length[9] and implicated Golgi transport in the correct positioning of the nucleus.[10] There is ample evidence that trafficking is coordinated with other cellular processes in higher eukaryotes as well. A comprehensive RNAi screen in *Drosophila* discovered that COPI coat proteins are important for cell division.[11] Also, vesicle trafficking has been linked to development[12] and to several signaling cascades.[13-16]

Accumulating evidence connects vesicular transport and gene expression as components of the trafficking machinery were shown to be necessary for the correct localization of a number of RNAs. Studies in two diverse systems (*Drosophila* and retrovirus-infected mammalian cells) have implicated a role for Rab11, which regulates traffic from the trans-Golgi to the plasma membrane and through recycling endosomes,[17,18] in RNA localization. During *Drosophila* oocyte development, *oskar* RNA localizes to the posterior pole and organizes the germ plasm.[19] However, in *rab11* loss-of-function mutants, *oskar* RNA does not completely reach the oocyte posterior pole.[20,21] Rab11-containing vesicles also transport retroviral RNAs: live imaging of RNAs from murine leukemia virus show co-localization of viral transcripts with the GTPase on recycling endosomes.[22] Likewise, components of the yeast secretory pathway are necessary for asymmetric RNA distribution, because mutations in a panel of secretory genes alter the localization of the transcription factor encoding RNA *ASH1*.[23]

The phenotypes observed in these studies, however, could be a result of defects in cytoskeleton integrity that arise from perturbations in vesicle trafficking, and therefore may reflect an indirect involvement of the secretory pathway. Indeed, *rab11* loss-of-function disrupts the organization of the microtubule plus ends,[20,24] and all yeast secretory mutations studied lead to defects in the actin cytoskeleton.[23] Recent work provides more convincing evidence for a direct involvement of the secretory pathway in the regulation of gene expression.[25] Two independent proteomic screens identified a significant number of trafficking regulators among the proteins associated with yeast total mRNA (**Table 1**, see legend).[25] In reciprocal experiments with two of the transport components (Vtc1 and Ubp3), hundreds of mRNAs were identified by DNA microarrays to be reproducibly associated with each protein.[25] Interestingly, a significant number of these RNAs encode proteins with specific sub-cellular localization, which coincides with the localization of the respective trafficking protein. For example, Vtc1, which is found at the vacuole and the endoplasmic reticulum (ER),[26] associates with transcripts of ER, membrane and vacuolar components. Thus, it appears that proteins with distinct roles in membrane trafficking can participate directly in the regulation of gene expression likely by transporting RNAs.

In yeast and mammalian cells, the processing of one RNA determines whether or not to activate the UPR, a crucial cell survival signaling cascade. It turns out that the expression of this key transcript in yeast is controlled by the vesicle trafficking machinery.[27] Here, we discuss the unexpected GTPase-dependent regulation of the UPR and speculate that it constitutes the biochemical mechanism to explain a functional link known to exist between these two key cellular processes.

## The UPR and Vesicle Trafficking

The UPR, triggered by accumulation of misfolded proteins in the ER, is an important cellular homeostatic mechanism implicated in a number of human diseases and pathologies such as neurodegeneration, diabetes, autoimmune response and cancer.[28-30] In *Saccharomyces cerevisiae* UPR, a highly conserved program in eukaryotes, the ER transmembrane kinase-endonuclease Ire1 activates this response via non-canonical splicing

of a transcription factor encoding RNA, *HAC1*.[31] The resulting *HAC1* junctions are next "ligated" by a tRNA ligase, Rlg1,[32] the mature *HAC1* mRNA is translated, and activates the expression of UPR target genes.

A number of studies have established a functional relationship between the UPR and vesicle trafficking. Chang et al.[33] and Leber et al.[34] reported activation of the UPR in the absence of chemical stress in secretory mutants defective in events extending from the ER to distal secretory compartments. Furthermore, when combined with *ire1*Δ or *hac1*Δ, the *sec* mutations were either partially lethal or led to a more extreme growth defect than *sec*⁻ alone.[33] Conversely, overexpression of *IRE1* or *HAC1* rescued the defects.[35,36] Interestingly, mutations in retrograde transport genes had no effect on the UPR.[34] One model that can account for all these observations is that mutations affecting exit from the ER and the exocytic pathway will perturb the balance between anterograde and retrograde transport. This will eventually lead to accumulation of Golgi-derived proteins in the ER,[37] thus overloading the folding capacity of the organelle (**Fig. 1**, dotted arrows). The cell would next activate its UPR, which increases the production of genes controlling secretory functions[38] in order to cope with the stress (**Fig. 1**, dotted arrows). Therefore, the functional relationship between trafficking and ER stress has been generally viewed as indirect and somewhat of an uneven dependency, where active UPR allows the cell to compensate for defects in its secretory pathway. However, we recently found evidence for a direct connection between vesicle trafficking and ER homeostasis (**Fig. 1**, solid arrows). This regulatory interplay is performed by the binding of the small GTPase Ypt1 to unspliced *HAC1* RNA and likely helps avert activation of the UPR in the absence of stress.

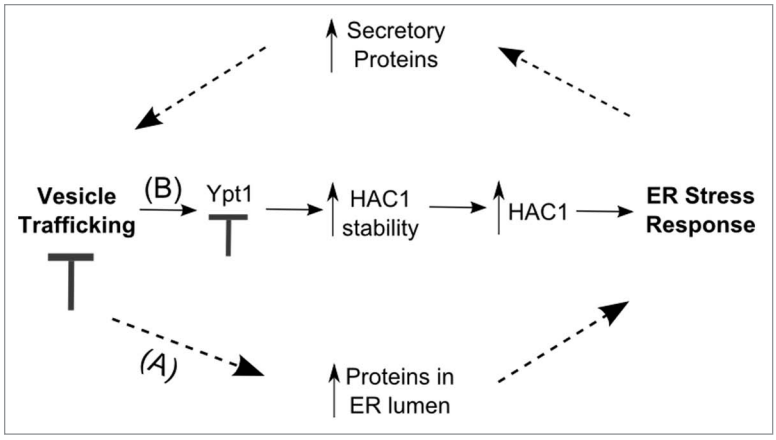


**Figure 1.** Crosstalk between vesicle trafficking and the unfolded protein response. (**A**) A block in the secretory pathway can indirectly activate the UPR (dotted arrows) by causing accumulation of proteins in the ER. The UPR, in turn, stimulates the expression of RNAs encoding secretory proteins, and will eventually alleviate the defect in transport. (**B**) Vesicle trafficking directly regulates the UPR: Ypt1 interacts with unspliced *HAC1* and leads to its degradation. A block in Ypt1 function will result in accumulation of *HAC1*, the RNA will get processed into Hac1 protein and eventually produce enough transcription factor to activate the UPR (solid arrows).

## Ypt1-Dependent Active Control of the UPR

We were interested in identifying *HAC1*-interacting proteins to gain new insights into UPR regulation, so we performed an protein microarray in vitro screen of the yeast proteome for *HAC1*-binding factors. We were surprised to find the RNA associating almost exclusively with small GTPases (**Table 1**, see legend).[27] Among the strongest interactors were three members of the Ypt family- Ypt1, Ypt7, and Ypt32. Since Ypt1 regulates ER-to-Golgi transport, perturbations of which trigger the UPR, we focused on the association between Ypt1 and *HAC1*. We confirmed the in vitro result by showing that the GTPase also interacts with unspliced *HAC1* in vivo, and observed that the interaction happens only in the absence of ER stress. The Ypt1-*HAC1* association could no longer be detected, once cells were treated with the UPR-inducing chemical DTT. These initial results suggested that there must be a more intimate link between vesicle trafficking and the UPR than previously anticipated. Further confirming a direct crosstalk were our findings that Ypt1 and *HAC1* do not associate in mutant strains lacking two genes required for proper UPR initiation, *IRE1* and *ADA5*,[31,39] and that Ypt1 interacts with Ada5.[27] Ada5 and Ire1 form a complex,[39] and Ire1 is an ER transmembrane protein; thus, we think it is very likely that an Ire1/Ada5/Ypt1-*HAC1* complex forms near the ER membrane. Consistent with this model, deleting the *HAC1* 3'UTR, which is required for efficient ER localization,[40] abolishes the Ypt1-*HAC1* interaction.[27] The precise roles of Ire1 and Ada5 in the GTPase-RNA association are currently unknown, but we speculate that these proteins may participate in the UPR-vesicle trafficking crosstalk by recruiting *HAC1* in proximity to Ypt1.

To determine the functional role of the Ypt1-*HAC1* interaction, we examined *HAC1* RNA levels in a *YPT1* knockdown strain. Unspliced *HAC1* copy number was ~2.5-fold higher in this mutant compared with wild type, and we found that this increase in expression is due to stabilization of the RNA.[27] The GTPase is also involved in recovery from ER stress, because cells with compromised *YPT1* expression recovered slower compared with wild type cells once the source of UPR was removed.[27] Therefore, there are physiological consequences of disturbing the Ypt1-*HAC1* interaction.

What could be the mechanism behind the destabilization of *HAC1* RNA by Ypt1? One possibility is that the RNA is degraded directly at the site of Ypt1-*HAC1* interaction, which we believe is the ER membrane (discussed above). An equally likely and not mutually exclusive model is that Ypt1-*HAC1* binding at the ER is followed by transport of the RNA away from the ER-localized processing machinery (Ire1 and Ada5) and close to RNA decay factors elsewhere in the cell (**Fig. 2**). We favor the second model, because it is

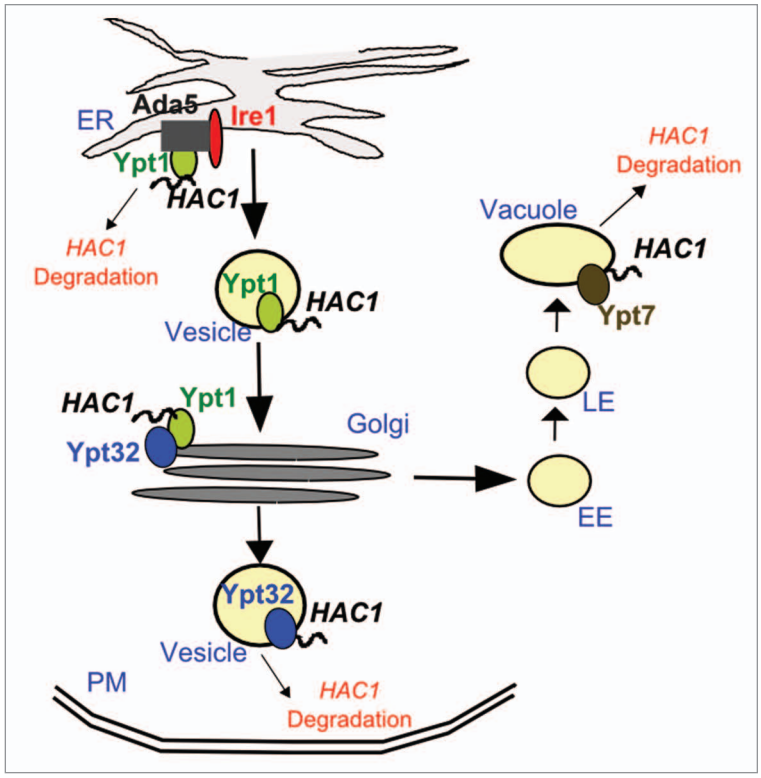


**Figure 2.** A putative mechanism for Ypt-dependent regulation of *HAC1* stability. Under normal growth conditions, Ypts mediate vesicle-assisted trafficking of unspliced *HAC1* away from the ER and the ER-localized Ire1/Ada5 complex to prevent unnecessary activation of the UPR. *HAC1* degradation may also be happening directly adjacent to the ER. Ypt GTPases 'communicate' with each other via interactions with common protein factors (e.g., GEFs, effectors, etc. not shown) and may utilize this crosstalk to direct *HAC1* localization in proximity to RNA decay factors for degradation. Additional adaptor proteins linking the *HAC1* RNA to the lipid membrane of the vesicle or mediating the Ypt-RNA interactions may be present but are not shown for simplicity. The *HAC1* RNA is depicted as a squiggly line. EE, early endosomes; LE, late endosomes; ER, endoplasmic reticulum; PM, plasma membrane.

consistent with our findings that two other Ypts (Ypt7 and 32), involved in trafficking to distal cellular compartments, also interact with unsliced *HAC1* RNA. Ypt7 orchestrates late endosome-to-vacuole trafficking and Ypt32 controls the intra-Golgi and post-Golgi steps of exocytosis. While we have not examined the interactions between *HAC1* and Ypts 7 and 32 beyond the initial screen, it is possible that Ypts 1/7/32 work together to coordinate the regulation of *HAC1* (**Fig. 2**). In support of this model, biochemical and genetic data suggest that small GTPases couple discrete vesicle trafficking steps. This GTPase crosstalk is established via interactions with common GEFs or downstream effectors (for extensive review, see refs. 41 and 42).

Secretory vesicles associated with a motor protein would provide a fast and efficient way to transport *HAC1* to distal cellular compartments. Since Ypt GTPases are key regulators of vesicle formation, trafficking, and docking, we anticipate that they could play a role in multiple aspects of *HAC1* trafficking. As no RNAs have been shown to interact directly with lipid membranes, the vesicle loading and trafficking of *HAC1* likely requires one or more adaptor proteins. Ypt GTPases, which are anchored to lipids via their di-prenylated C-termini, or Ypt protein interactors that have the capacity to interact with both nucleic acids and membranes are natural candidates for such mediators (it should be noted that none of the currently documented Ypt binding partners have been shown to associate with both membranes and RNA). In addition to acting as adaptors stabilizing the *HAC1*-vesicle interaction, Ypts may also be directly involved in the recruitment of motor proteins that transport the RNA-containing vesicle. Indeed, one of the three Ypts associating with *HAC1*, Ypt32, interacts with the class V myosin motor Myo2 during secretion.[43] Directed vesicle-mediated transport of *HAC1* away from the ER aided by *HAC1*-interacting GTPases would provide an efficient means for the cell to keep its UPR "off" in the absence of stress stimuli.

Our model (**Fig. 2**) would predict that defects in vesicle trafficking would prevent Ypt-dependent *HAC1* RNA localization to decay factors and lead to stabilization and accumulation of unspliced *HAC1* near the ER and the ER-localized *HAC1* splicing machinery (**Fig. 1**, solid arrows). Amassed *HAC1* RNA would then be processed by Ire1 to produce functional Hac1 protein that will eventually reach a critical threshold and activate the UPR. In agreement with this scenario, we observed increased amounts of spliced *HAC1* RNA, when we knocked down *YPT1*.[27] Such direct regulatory relationship between vesicle trafficking and ER stress would provide an efficient way for the cell to communicate defects in its secretory pathway to ER surveillance and enable a robust response to perturbations of cellular homeostasis.

Many questions remain to be addressed. As Ypt1-dependent recruitment of *HAC1* to decay factors is a plausible mechanism of how the GTPase regulates RNA stability, it will be important to test if Ypt1 interacts physically and/or genetically with known members of the yeast decay machinery, in order to start dissecting the precise features of the process. Also, the recruitment of *HAC1* could be either active, i.e., involving a physical association of the RNA with the GTPase and subsequent directional localization of the RNA, or indirect, in which case the RNA 'hitches' a ride on a secretory vesicle along with other cargo trafficked between the ER and Golgi. Our data do not distinguish between the two possibilities, since we purified the proteins used for generating protein microarrays for the initial screen from yeast[25] and cannot exclude co-purification of proteins. Further, we suspect that the Ypt1-*HAC1* interaction takes place close to the ER membrane and is assisted by the Ire1/Ada5 complex,

but this model remains to be tested. Also, the regulatory roles of the other secretory proteins identified in the screen (e.g., Ypt7 and Ypt32) should be established. If these GTPases are important in regulating the RNA stability of *HAC1* similar to Ypt1, it will be interesting to determine if Ypts communicate with each other to control the fate of *HAC1*. Lastly, Ypts 1, 7 and 32 share 60–70% homology with and function in the same transport compartments as mammalian Rabs 1, 7 and 11, respectively.[41] Future studies should investigate whether mammalian Rabs play a direct role in UPR regulation analogous to their yeast counterparts by testing for interactions between Rabs and the mammalian ortholog of *HAC1*, *XBP1*. Despite the open questions, it is clear that there is a direct link between the secretory pathway and the UPR and that vesicle trafficking plays an active role in the regulation of ER homeostasis.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### References


1. Soldati T, Shapiro AD, Svejstrup AB, Pfeffer SR. Membrane targeting of the small GTPase Rab9 is accompanied by nucleotide exchange. Nature 1994; 369:76-8; PMID:8164745; http://dx.doi.org/10.1038/369076a0
2. Ullrich O, Horiuchi H, Bucci C, Zerial M. Membrane association of Rab5 mediated by GDP-dissociation inhibitor and accompanied by GDP/GTP exchange. Nature 1994; 368:157-60; PMID:8139660; http://dx.doi.org/10.1038/368157a0
3. Rak A, Pylypenko O, Durek T, Watzke A, Kushnir S, Brunsveld L, et al. Structure of Rab GDP-dissociation inhibitor in complex with prenylated YPT1 GTPase. Science 2003; 302:646-50; PMID:14576435; http://dx.doi.org/10.1126/science.1087761
4. Chavrier P, Gorvel JP, Stelzer E, Simons K, Gruenberg J, Zerial M. Hypervariable C-terminal domain of rab proteins acts as a targeting signal. Nature 1991; 353:769-72; PMID:1944536; http://dx.doi.org/10.1038/353769a0
5. Stenmark H, Valencia A, Martinez O, Ullrich O, Goud B, Zerial M. Distinct structural elements of rab5 define its functional specificity. EMBO J 1994; 13:575-83; PMID:8313902
6. ten Klooster JP, Hordijk PL. Targeting and localized signalling by small GTPases. Biol Cell 2007; 99:1-12; PMID:17155934; http://dx.doi.org/10.1042/BC20060071
7. Pfeffer S. A model for Rab GTPase localization. Biochem Soc Trans 2005; 33:627-30; PMID:16042559; http://dx.doi.org/10.1042/BST0330627
8. Pfeffer S, Aivazian D. Targeting Rab GTPases to distinct membrane compartments. Nat Rev Mol Cell Biol 2004; 5:886-96; PMID:15520808; http://dx.doi.org/10.1038/nrm1500
9. Rog O, Smolikov S, Krauskopf A, Kupiec M. The yeast VPS genes affect telomere length regulation. Curr Genet 2005; 47:18-28; PMID:15551135; http://dx.doi.org/10.1007/s00294-004-0548-y
10. Ohya Y, Sese J, Yukawa M, Sano F, Nakatani Y, Saito TL, et al. High-dimensional and large-scale phenotyping of yeast mutants. Proc Natl Acad Sci USA 2005; 102:19015-20; PMID:16365294; http://dx.doi.org/10.1073/pnas.0509436102
11. Eggert US, Kiger AA, Richter C, Perlman ZE, Perrimon N, Mitchison TJ, et al. Parallel chemical genetic and genome-wide RNAi screens identify cytokinesis inhibitors and targets. PLoS Biol 2004; 2:e379; PMID:15547975; http://dx.doi.org/10.1371/journal.pbio.0020379
12. Entchev EV, Schwabedissen A, González-Gaitán M. Gradient formation of the TGF-beta homolog Dpp. Cell 2000; 103:981-91; PMID:11136982; http://dx.doi.org/10.1016/S0092-8674(00)00200-2
13. Alvarez-Dominguez C, Stahl PD. Interferon-gamma selectively induces Rab5a synthesis and processing in mononuclear cells. J Biol Chem 1998; 273:33901-4; PMID:9852039; http://dx.doi.org/10.1074/jbc.273.51.33901
14. Barbieri MA, Kohn AD, Roth RA, Stahl PD. Protein kinase B/akt and rab5 mediate Ras activation of endocytosis. J Biol Chem 1998; 273:19367-70; PMID:9677351; http://dx.doi.org/10.1074/jbc.273.31.19367
15. Barbieri MA, Roberts RL, Gumusboga A, Highfield H, Alvarez-Dominguez C, Wells A, et al. Epidermal growth factor and membrane trafficking. EGF receptor activation of endocytosis requires Rab5a. J Cell Biol 2000; 151:539-50; PMID:11062256; http://dx.doi.org/10.1083/jcb.151.3.539
16. Lanzetti L, Rybin V, Malabarba MG, Christoforidis S, Scita G, Zerial M, et al. The Eps8 protein coordinates EGF receptor signalling through Rac and trafficking through Rab5. Nature 2000; 408:374-7; PMID:11099046; http://dx.doi.org/10.1038/35042605
17. Chen W, Feng Y, Chen DY, Wandinger-Ness A. Rab11 is required for trans-golgi network-to-plasma membrane transport and a preferential target for GDP dissociation inhibitor. Mol Biol Cell 1998; 9:3241-57; PMID:9802909
18. Lin SXH, Teter K, Young JJ, Moore HP. Role of rab11 in TF recycling and transport between TGN and recycling endosomes. Mol Biol Cell 1996; 7:3438
19. Ephrussi A, Dickinson LK, Lehmann R. Oskar organizes the germ plasm and directs localization of the posterior determinant nanos. Cell 1991; 66:37-50; PMID:2070417; http://dx.doi.org/10.1016/0092-8674(91)90137-N
20. Dollar G, Struckhoff E, Michaud J, Cohen RS. Rab11 polarization of the Drosophila oocyte: a novel link between membrane trafficking, microtubule organization, and oskar mRNA localization and translation. Development 2002; 129:517-26; PMID:11807042
21. Jankovics F, Sinka R, Erdélyi M. An interaction type of genetic screen reveals a role of the Rab11 gene in oskar mRNA localization in the developing Drosophila melanogaster oocyte. Genetics 2001; 158:1177-88; PMID:11454766
22. Basyuk E, Galli T, Mougel M, Blanchard JM, Sitbon M, Bertrand E. Retroviral genomic RNAs are transported to the plasma membrane by endosomal vesicles. Dev Cell 2003; 5:161-74; PMID:12852860; http://dx.doi.org/10.1016/S1534-5807(03)00188-6
23. Aronov S, Gerst JE. Involvement of the late secretory pathway in actin regulation and mRNA transport in yeast. J Biol Chem 2004; 279:36962-71; PMID:15192110; http://dx.doi.org/10.1074/jbc.M402068200
24. Zhang H, Squirrell JM, White JG. RAB-11 permissively regulates spindle alignment by modulating metaphase microtubule dynamics in Caenorhabditis elegans early embryos. Mol Biol Cell 2008; 19:2553-65; PMID:18385514; http://dx.doi.org/10.1091/mbc.E07-09-0862
25. Tsvetanova NG, Klass DM, Salzman J, Brown PO. Proteome-wide search reveals unexpected RNA-binding proteins in Saccharomyces cerevisiae. PLoS ONE 2010; 5:5; PMID:20844764; http://dx.doi.org/10.1371/journal.pone.0012671
26. Cherry JM, Ball C, Weng S, Juvik G, Schmidt R, Adler C, et al. Genetic and physical maps of Saccharomyces cerevisiae. Nature 1997; 387(Suppl):67-73; PMID:9169866; http://dx.doi.org/10.1038/43025
27. Tsvetanova NG, Riordan DP, Brown PO. The yeast Rab GTPase Ypt1 modulates unfolded protein response dynamics by regulating the stability of HAC1 RNA. PLoS Genet 2012; 8:e1002862; PMID:22844259; http://dx.doi.org/10.1371/journal.pgen.1002862
28. Austin RC. The unfolded protein response in health and disease. Antioxid Redox Signal 2009; 11:2279-87; PMID:19485711; http://dx.doi.org/10.1089/ars.2009.2686
29. Zhang K, Kaufman RJ. The unfolded protein response: a stress signaling pathway critical for health and disease. Neurology 2006; 66(Suppl 1):S102-9; PMID:16432136; http://dx.doi.org/10.1212/01.wnl.0000192306.98198.ec
30. Kaufman RJ. Orchestrating the unfolded protein response in health and disease. J Clin Invest 2002; 110:1389-98; PMID:12438434
31. Sidrauski C, Walter P. The transmembrane kinase Ire1p is a site-specific endonuclease that initiates mRNA splicing in the unfolded protein response. Cell 1997; 90:1031-9; PMID:9323131; http://dx.doi.org/10.1016/S0092-8674(00)80369-4
32. Sidrauski C, Cox JS, Walter P. tRNA ligase is required for regulated mRNA splicing in the unfolded protein response. Cell 1996; 87:405-13; PMID:8898194; http://dx.doi.org/10.1016/S0092-8674(00)81361-6
33. Chang HJ, Jesch SA, Gaspar ML, Henry SA. Role of the unfolded protein response pathway in secretory stress and regulation of INO1 expression in Saccharomyces cerevisiae. Genetics 2004; 168:1899-913; PMID:15371354; http://dx.doi.org/10.1534/genetics.104.032961
34. Leber JH, Bernales S, Walter P. IRE1-independent gain control of the unfolded protein response. PLoS Biol 2004; 2:E235; PMID:15314654; http://dx.doi.org/10.1371/journal.pbio.0020235
35. Higashio H, Kohno K. A genetic link between the unfolded protein response and vesicle formation from the endoplasmic reticulum. Biochem Biophys Res Commun 2002; 296:568-74; PMID:12176018; http://dx.doi.org/10.1016/S0006-291X(02)00923-3
36. Sato M, Sato K, Nakano A. Evidence for the intimate relationship between vesicle budding from the ER and the unfolded protein response. Biochem Biophys Res Commun 2002; 296:560-7; PMID:12176017; http://dx.doi.org/10.1016/S0006-291X(02)00922-1
37. Cole NB, Ellenberg J, Song J, DiEuliis D, Lippincott-Schwartz J. Retrograde transport of Golgi-localized proteins to the ER. J Cell Biol 1998; 140:1-15; PMID:9425149; http://dx.doi.org/10.1083/jcb.140.1.1
38. Travers KJ, Patil CK, Wodicka L, Lockhart DJ, Weissman JS, Walter P. Functional and genomic analyses reveal an essential coordination between the unfolded protein response and ER-associated degradation. Cell 2000; 101:249-58; PMID:10847680; http://dx.doi.org/10.1016/S0092-8674(00)80835-1

39. Welihinda AA, Tirasophon W, Kaufman RJ. The transcriptional co-activator ADA5 is required for HAC1 mRNA processing in vivo. J Biol Chem 2000; 275:3377-81; PMID:10652329; http://dx.doi.org/10.1074/jbc.275.5.3377
40. Aragón T, van Anken E, Pincus D, Serafimova IM, Korennykh AV, Rubio CA, et al. Messenger RNA targeting to endoplasmic reticulum stress signalling sites. Nature 2009; 457:736-40; PMID:19079237; http://dx.doi.org/10.1038/nature07641
41. Segev N. Ypt/rab gtpases: regulators of protein trafficking. Sci STKE 2001; 2001:re11; PMID:11579231; http://dx.doi.org/10.1126/stke.2001.100.re11
42. Segev N. Ypt and Rab GTPases: insight into functions through novel interactions. Curr Opin Cell Biol 2001; 13:500-11; PMID:11454458; http://dx.doi.org/10.1016/S0955-0674(00)00242-8
43. Lipatova Z, Tokarev AA, Jin Y, Mulholland J, Weisman LS, Segev N. Direct interaction between a myosin V motor and the Rab GTPases Ypt31/32 is required for polarized secretion. Mol Biol Cell 2008; 19:4177-87; PMID:18653471; http://dx.doi.org/10.1091/mbc.E08-02-0220