PANCREAPEDIA
Exocrine Pancreas Knowledge Base

APA AMERICAN PANCREATIC ASSOCIATION

Rab27

Yanan Hou, Xuequn Chen, John A Williams

Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI 48109

Email: jawillms@umich.edu

Version 1.0, August 26, 2010 [DOI: 10.3998/panc.2010.14]

Gene Symbols: Rab27A, Rab27B

1. General Function

Rab proteins are monomeric Ras-like small GTPases and constitute the largest family of the known membrane trafficking proteins. Rabs act as molecular switches cycling between GTP-bound active and GDP-bound inactive conformations (1, 2). Among the Rab proteins, Rab27 proteins, along with Rab3 and Rab26, play important roles in regulation of various regulated secretion events (3). There are two isoforms of Rab27, Rab27A and Rab27B, which were originally cloned from human melanoma cells, melanocytes and platelet cytosol (4, 5). Human Rab27A and Rab27B share 66% identity at the nucleotide level in their open reading frames (ORFs) and 71% identity in amino acid sequence (Figure 1). Variation is greatest in the carboxyl terminal. It is not clear whether the two Rab27 isoforms mediate different actions or are expressed in different cell types or both. It appears that Rab27A and 27B have been fully divided from each other in evolutionary time since amphibians, as the two Rab27 isoforms of Xenopus similarly show 73% identity in amino acid sequence. Appendix 1 shows the protein sequences of Rab27A and Rab27B from all reported species. Zebrafish, Drosophila and C. elegans have only one form of Rab27, which is most similar to human Rab27A.

Rab proteins require prenylation to properly exert their function. Rab27 proteins bear Cys-X-Cys at the C terminal, geranylgeranyl residues can be attached to the two cysteines by Rab geranylgeranyl transferase (RGGT), also called type II geranylgeranyl transferase (GGT II) (6). The newly synthesized Rab proteins are first recognized and bound by Rab escort protein (REP) and then are presented to RGGT for the posttranslational modification (7). In Figure 1, the REP and RGGT recognition motifs of human Rab27A and 27B were highlighted.

Rab27A

Mutations in the Rab27A gene cause type 2 Griscelli Syndrome (GS2), a rare, autosomal recessive disorder that results in pigmentary dilution of the skin and hair with the presence of large clumps of pigment in hair shafts and an accumulation of melanosomes in melanocytes. Most patients also develop an uncontrolled T-lymphocyte and macrophage activation syndrome known as haemophagocytic syndrome (8). A mutation in the mouse ortholog Rab27a is responsible for the phenotypes in *ashen* mice, including uneven release of pigment into the hair bulb and a lightened coat color, as well as the

reduction in the number of platelet dense granules in *ashen* mice. This single point mutation prevents the proper splicing of Rab27A transcripts, leading to Rab27A deficiency (9). Subsequent studies showed that Rab27A colocalizes with melanosomes and regulates melanosome transport in melanocytes (10, 11) and that Rab27A is involved in the regulated granule exocytosis in cytotoxic T lymphocytes (CTLs) (12, 13). Pigment granules in melanocytes from ashen mice and GS patients show perinuclear clustering. Reexpression of Rab27A in GS melanocytes restored the normal distribution of melanosomes (10, 11). CTLs from *ashen* mice and GS patients are unable to kill target cells or to secrete granzyme A and hexosaminidase, although these CTLs show normal levels of perforin and granzymes A and B and normal-appearing perforin-positive granules (8, 12, 13), indicating that Rab27A is required for a late step in granule exocytosis in CTLs.

In melanocytes, Rab27A binds to melanosomes and then recruits its effector melanophilin/Slac2-a, which in turn recruits myosin-Va, an actin-based molecular motor. Thus, melanophilin/Slac2-a acts as a linker between Rab27A and myosin-Va. It binds to Rab27A in a GTP-dependent fashion through its amino terminus, and to myosin-Va through its carboxy terminus (14-17). Mutations in the myosin-Va gene (MYO5A) cause type 1 Griscelli Syndrome (GS1) (18); the corresponding coat-color mutant mouse *dilute* exhibits a defect in melanosome transport and also bears missense mutations in the globular tail of myosin-Va or has F-exon deletion in the myosin-Va gene (19, 20). The third type of Griscelli syndrome (GS3) was found to be caused by the mutation in the melanophilin/Slac2-a (20). The mutation of melanophilin/Slac2-a leads to the partial albinism in *leaden* color mutant mice (21).

Rab27A and its effector MyRIP (also known as Slac2-c) were reported to be associated with large dense core granules in adrenal chromaffin cells and pheochromocytoma PC12 cells and to control the secretory activity in a manner that depends on the state of the actin cortex (22). Overexpression of Rab27A in PC12 cells promoted high KCl-dependent secretion of neuropeptide Y (23). Rab27A was also found to be expressed on dense-core vesicles and play a key role in the docking step of dense-core vesicle exocytosis in PC12 cells (24). Silencing of Rab27A significantly decreased the number of dense-core vesicles docked to the plasma membrane without altering the kinetics of individual exocytotic events (24).

In pancreatic beta-cell, Rab27A was shown to mediate the tight docking of insulin granules to the plasma membrane upon the high glucose stimulation (25). Ashen mice showed glucose intolerance after a glucose load without signs of insulin resistance in peripheral tissues or insulin deficiency in the pancreas. The docking of insulin granules on the plasma membrane and the replenishment of docked granules during glucose stimulation were markedly reduced in *ashen* mouse pancreatic islets. In addition, Rab27A was shown to regulate the exocytosis of insulin-containing dense-core granules by forming a complex with granuphilin in pancreatic beta-cells (26). It was further demonstrated that Rab27A exerts dual roles in glucose-mediated insulin granule exocytosis, facilitating refilling of releasable granule pools while also limiting the rate of release from these pools (27).

Rab3 GDP/GTP exchange protein (Rab3GEP), previously isolated as a guanine nucleotide exchange factor (GEF) for Rab3, was recently identified as the GEF required for the activation of Rab27A in melanocytes (28). Similar to Rab27A-deficient *ashen* melanocytes, Rab3GEP-depleted cells show both clustering of melanosomes in the perinuclear area and loss of the Rab27a effector melanophilin. Rab27A-GTP levels are decreased in cells lacking Rab3GEP. Recombinant Rab3GEP exhibits guanine nucleotide exchange activity against both Rab27A and Rab27B in vitro, in addition to its previously documented activity against Rab3 (28). These data suggest that members of related but functionally distinct Rab subfamilies can be controlled by common activators.

A TBC (Tre2/Bub2/Cdc16) domain-containing protein, EPI64 was identified as a specific GTPase-activating protein (GAP) for Rab27A by a functional interaction screening (29). EPI64 showed GAP activity against Rab27A both in vivo and in vitro. In

addition, a homologue of EPI64, EPI64B also exhibited Rab27A GAP activity *in vitro*.

Rab27B

The expression of the other Rab27 member, Rab27B was also detected in melanocytes and GFP-tagged Rab27B was shown to co-localize with melanosome marker protein; transient overexpression of the dominant negative forms of Rab27B caused diminution in both numbers and length of dendrites of melanocytes (30).Transgenic Rab27B can rescue *ashen* coat color, similar to Rab27A, and melanocytes derived from these transgenic mice exhibit widespread peripheral distribution of melanosomes instead of the perinuclear clumping observed in *ashen* melanocytes. Finally, transient expression in *ashen* melanocytes of Rab27A or Rab27B, but not other Rab's, restores peripheral distribution of melanosomes, indicating that Rab27B can be functionally redundant for Rab27A (31). Consistently, up-regulation of Rab27B was detected in the melanocytes from a Griscelli syndrome type II patient, which can partially compensate for the deletion of Rab27A (32).

Rab27B has been found in a large number of secretory cells (Table 1). In the most complete analysis, transgenic mice, generated by replacing the Rab27B gene with reporter gene LacZ under control of the endogenous promoter, indicated that Rab27B is widely expressed in secretory cells, neurons and cells involved in surface protection and mechanical extension (33). Rab27B was found to be abundantly expressed in pituitary tissue, where Rab27A and Rab27B are differentially expressed in cell types that secrete different peptide hormones (34). Rab27B also associates with secretory granules and the linker protein, granuphilin in the pituitary endocrine cell line AtT20. Furthermore, over-expression of the inactive mutant, Rab27B N133I, significantly inhibited basal and forskolin-induced ACTH secretion from AtT20 cells, indicating that Rab27B is involved in pituitary hormone secretion (34).

Rab27B is required for proplatelet formation and its expression in these cells is regulated by the transcription factor nuclear factor-erythroid 2 (NF-E2) (35). Rab27B knockout (KO) mice exhibit significant hemorrhagic disease in contrast to *ashen* mice, which do not. In vitro assays demonstrated impaired platelet aggregation with collagen and U46619 and reduced numbers and secretion of dense granules in Rab27B KO strain (36), suggesting that Rab27B is a key regulator of dense granule secretion in platelets and this regulation might be through binding to its effector Munc13-4 (37). Bone marrow derived mast cells (BMMC) from Rab27B KO mice also exhibit mild clustering of granules, indicating that Rab27B may play a crucial role in mast cell degranulation and that their action regulates the transition from microtubule to actin-based motility (38).

In the urinary system, Rab27B was found to associate with the cytoplasmic face of the fusiform vesicles and to be involved in targeting uroplakins to urothelial apical membranes umbrella cells of bladder epithelium (39). Rab27B was also required for the exocytosis of type 1 fimbriated uropathogenic Escherichia coli (UPEC) from infected bladder epithelial cells (BECs) (40, 41).

In several most recent studies, Rab27B was shown to be required for antrograde transport of neurotrophin receptor TrkB in axons (42); Rab27A and Rab27B deficiencies both impaired azurophilic granule exocytosis in neutrophils with the data indicating that the two Rab27 isoforms play independent roles in neutrophil exocytosis (43). Rab27 isoforms have also been found to function in multivesicular endosomes (MVE) docking at the plasma membrane and control different steps of the exosome secretion pathway (44). Finally, Rab27B was shown to regulate invasive growth and metastasis in estrogen receptor (ER)-positive breast cancer cell lines, by mediating the secretion of a key proinvasive growth regulator, heat-shock protein 90α (45). Clinical specimens also demonstrated that presence of endogenous Rab27B mRNA and protein was associated with lymph node metastasis and differentiation grade in ER-positive human breast tumors (45). These studies broadened the role of Rab27A and Rab27B in intracellular membrane trafficking.

2. Pancreatic Information

Both Rab27A and 27B are present in rodent pancreas, with Rab27A primarily in islets of Langerhans (25, 26) and Rab27B in acinar cells (46). Rab27B was originally identified in acinar cells, by MS/MS studies of proteins on the zymogen granule (ZG) membrane (46). This identification was further confirmed by western blot, immunofluorescence and quantitative proteomic analysis (47, 48). Portease protection studies showed that Rab27B was on the external surface of the zymogen granules (48). Figure 2 shows the localization of Rab27B in rat pancreatic acinus and on isolated zymogen granules. Over-expression of constitutively active Rab27B enhanced CCK-induced amylase release from isolated rat pancreatic acini, while dominant negative Rab27B inhibited amylase release. These results demonstrate that Rab27b is present on ZGs and plays an important role in regulating acinar exocytosis. Whether Rab27A is present in acinar cells is somewhat controversial. It has not been recognized on zymogen granules by MS or WB. It may be present on lysosomes or other intracellular vesicular compartments (G. Groblewski, personal communication).

A putative Rab27B effector protein, Synaptotagmin-like protein 1 (Slp1) was found to be abundantly expressed in the zymogen granule membranes in pancreatic acinar cells by MS and western blotting (48). Slp1 was shown to interact with Rab27B in vivo and both proteins were co-localized on zymogen granules (49). Fasted Slp1 knockout mice showed an increased number of zymogen granules in the pancreatic acinar cells, indicating that Slp1 is part of the machinery of amylase secretion by the exocrine pancreas (49).

Rab27B also appears to play a similar role in other exocrine glands as well. In a recent study in salivary gland, Rab27B was demonstrated to form complex with an effector Slac2-c on the secretory granules in rat parotid acinar cells (50). Upon isoproterenol (IPR) stimulation, Rab27B translocated from secretory granules to the subapical region, and then was released into the cytosol after longer time IPR treatment (51). The similar redistribution pattern of Rab27-specific effector Slac2-c was found in rat parotid acinar cells upon IPR stimulation (52). Blockage of Rab27B by specific antibody inhibited IPR -stimulated amylase release from streptolysin O-permeabilized parotid acinar cells (50).

Approximately half of Rab27B in acinar cells appears to be GTP-liganded (unpublished data). Studies reported in abstract form by us have identified the presence of two potential Rab27B GAPs, EPI64 and EPI64B in mouse pancreatic acinar cells and shown that overexpression of EPI64B reduced the active form of Rab27B.

3. Tools for Study

a. cDNA

cDNA clones for human Rab27a and Rab27b in pcDNA3.1 are available from the Missoury S&T cDNA Resource (www.cdna.org). A number of investigators have published studies using constitutively active or dominant negative mutant plasmids based on mutating residues important in Ras (30, 34, 46, 53, 54).

b. Antibodies

Several antibodies against both Rab27a and 27b are available from Santa Cruz, BD and Synaptic Systems. We have had success for Western blotting and IHC using a rabbit Ab against a GST fusion protein of Rab27b (46, 47) that had been generated by Dr Tetsuro Izumi's laboratory (34). The rabbit polyclonal Abs for Rab27A and 27B available from Synaptic Systems have worked for Western blotting, but not for IHC. We have not tested the Santa Cruz antibodies.

c. Viral vectors

Adenoviral vectors for Xpress-tagged wild type, constitutively active (Q78L) and dominant negative (N133I) Rab27b have been used in rat pancreatic acini (46). They are available from the authors with permission from Dr Tetsuro Izumi (34). The Xpress tag can be visualized for WB or immunohistochemistry by use of a mouse

monoclonal antibody (Cat. R910-25) from Invitrogen.

d. Mice Models

Ashen mice have a naturally occurring deletion of Rab27a and are available from JAX. Mice with genetic deletion of Rab27b have been reported by two laboratories (33, 36). The Miguel Seabra group has also bred a combined ashen and Rab27b knockout mice to generate a double knockout of Rab27a and 27b. Rab 27b KO and Rab27 double KO have impaired platelet function leading to hemorrhagic disease (36).

e. Assay

Assay for active Rab27b. GTP-bound active Rab27 isoforms preferentially bind to the synaptotagmin-like protein (Slp)-homology domain (SHD) of its specific effector, Slac2-b. By use of glutathione-Sepharose beads (Amersham Biosciences) coated with GST-SHD of Slac2-b, the active form of Rab27B will be pulled down and can then be analyzed by immunoblotting with Ab specific for Rab27B (55). We have used this assay with GST-SHD to determine active state of Rab27B in mouse acini

4. Reference

1. **Zerial M and McBride H.** Rab proteins as membrane organizers. *Nat Rev Mol Cell Biol* 2: 107-117, 2001. **PMID:**11252952
2. **Fukuda M.** Regulation of secretory vesicle traffic by Rab small GTPases. *Cell Mol Life Sci* 65: 2801-2813, 2008. **PMID:**18726178
3. **Stenmark H.** Rab GTPases as coordinators of vesicle traffic. *Nat Rev Mol Cell Biol* 10: 513-525, 2009. **PMID:**19603039
4. **Nagata K, Itoh H, Katada T, Takenaka K, Ui M, Kaziro Y, and Nozawa Y.** Purification, identification, and characterization of two GTP-binding proteins with molecular weights of 25,000 and 21,000 in human platelet cytosol. One is the rap1/smg21/Krev-1 protein and the other is a novel GTP-binding protein. *J Biol Chem* 264: 17000-17005, 1989. **PMID:**2507536
5. **Chen D, Guo J, Miki T, Tachibana M, and Gahl WA.** Molecular cloning and characterization of rab27a and rab27b, novel human rab proteins shared by melanocytes and platelets. *Biochem Mol Med* 60: 27-37, 1997. **PMID:**9066979
6. **Seabra MC, Goldstein JL, Sudhof TC, and Brown MS.** Rab geranylgeranyl transferase. A multisubunit enzyme that prenylates GTP-binding proteins terminating in Cys-X-Cys or Cys-Cys. *J Biol Chem* 267: 14497-14503, 1992. **PMID:**1321151
7. **Seabra MC, Brown MS, Slaughter CA, Sudhof TC, and Goldstein JL.** Purification of component A of Rab geranylgeranyl transferase: possible identity with the choroideremia gene product. *Cell* 70: 1049-1057, 1992. **PMID:**1525821
8. **Menasche G, Pastural E, Feldmann J, Certain S, Ersoy F, Dupuis S, Wulffraat N, Bianchi D, Fischer A, Le Deist F, and de Saint Basile G.** Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. *Nat Genet* 25: 173-176, 2000. **PMID:**10835631
9. **Wilson SM, Yip R, Swing DA, O'Sullivan TN, Zhang Y, Novak EK, Swank RT, Russell LB, Copeland NG, and Jenkins NA.** A mutation in Rab27a causes the vesicle transport defects observed in ashen mice. *Proc Natl Acad Sci U S A* 97: 7933-7938, 2000. **PMID:**10859366
10. **Bahadoran P, Aberdam E, Mantoux F, Busca R, Bille K, Yalman N, de Saint-Basile G, Casaroli-Marano R, Ortonne JP, and Ballotti R.** Rab27a: A key to melanosome transport in human melanocytes. *J Cell Biol* 152: 843-850, 2001. **PMID:**11266474
11. **Hume AN, Collinson LM, Rapak A, Gomes AQ, Hopkins CR, and Seabra MC.** Rab27a regulates the peripheral distribution of melanosomes in melanocytes. *J Cell Biol* 152: 795-808, 2001. **PMID:**11266470
12. **Haddad EK, Wu X, Hammer JA, 3rd, and Henkart PA.** Defective granule exocytosis in Rab27a-deficient lymphocytes from Ashen mice. *J Cell Biol* 152: 835-842, 2001. **PMID:**11266473
13. **Stinchcombe JC, Barral DC, Mules EH, Booth S, Hume AN, Machesky LM, Seabra MC, and Griffiths GM.** Rab27a is required for regulated secretion in cytotoxic T lymphocytes. *J Cell Biol* 152: 825-834, 2001. **PMID:**11266472
14. **Fukuda M, Kuroda TS, and Mikoshiba K.** Slac2-a/melanophilin, the missing link between Rab27 and myosin Va: implications of a tripartite protein complex for melanosome transport. *J Biol Chem* 277: 12432-12436, 2002. **PMID:**11856727

15. **Nagashima K, Torii S, Yi Z, Igarashi M, Okamoto K, Takeuchi T, and Izumi T.** Melanophilin directly links Rab27a and myosin Va through its distinct coiled-coil regions. *FEBS Lett* 517: 233-238, 2002. **PMID:**12062444
16. **Strom M, Hume AN, Tarafder AK, Barkagianni E, and Seabra MC.** A family of Rab27-binding proteins. Melanophilin links Rab27a and myosin Va function in melanosome transport. *J Biol Chem* 277: 25423-25430, 2002. **PMID:**11980908
17. **Wu XS, Rao K, Zhang H, Wang F, Sellers JR, Matesic LE, Copeland NG, Jenkins NA, and Hammer JA, 3rd.** Identification of an organelle receptor for myosin-Va. *Nat Cell Biol* 4: 271-278, 2002. **PMID:**11887186
18. **Pastural E, Barrat FJ, Dufourcq-Lagelouse R, Certain S, Sanal O, Jabado N, Seger R, Griscelli C, Fischer A, and de Saint Basile G.** Griscelli disease maps to chromosome 15q21 and is associated with mutations in the myosin-Va gene. *Nat Genet* 16: 289-292, 1997. **PMID:**9207796
19. **Fukuda M and Kuroda TS.** Missense mutations in the globular tail of myosin-Va in dilute mice partially impair binding of Slac2-a/melanophilin. *J Cell Sci* 117: 583-591, 2004. **PMID:**14730011
20. **Menasche G, Ho CH, Sanal O, Feldmann J, Tezcan I, Ersoy F, Houdusse A, Fischer A, and de Saint Basile G.** Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F-exon deletion (GS1). *J Clin Invest* 112: 450-456, 2003. **PMID:**12897212
21. **Matesic LE, Yip R, Reuss AE, Swing DA, O'Sullivan TN, Fletcher CF, Copeland NG, and Jenkins NA.** Mutations in Mlph, encoding a member of the Rab effector family, cause the melanosome transport defects observed in leaden mice. *Proc Natl Acad Sci U S A* 98: 10238-10243, 2001. **PMID:**11504925
22. **Desnos C, Schonn JS, Huet S, Tran VS, El-Amraoui A, Raposo G, Fanget I, Chapuis C, Menasche G, de Saint Basile G, Petit C, Cribier S, Henry JP, and Darchen F.** Rab27A and its effector MyRIP link secretory granules to F-actin and control their motion towards release sites. *J Cell Biol* 163: 559-570, 2003. **PMID:**14610058
23. **Fukuda M, Kanno E, Saegusa C, Ogata Y, and Kuroda TS.** Slp4-a/granuphilin-a regulates dense-core vesicle exocytosis in PC12 cells. *J Biol Chem* 277: 39673-39678, 2002. **PMID:**12176990
24. **Tsuboi T and Fukuda M.** Rab3A and Rab27A cooperatively regulate the docking step of dense-core vesicle exocytosis in PC12 cells. *J Cell Sci* 119: 2196-2203, 2006. **PMID:**16684812
25. **Kasai K, Ohara-Imaizumi M, Takahashi N, Mizutani S, Zhao S, Kikuta T, Kasai H, Nagamatsu S, Gomi H, and Izumi T.** Rab27a mediates the tight docking of insulin granules onto the plasma membrane during glucose stimulation. *J Clin Invest* 115: 388-396, 2005. **PMID:**15690086
26. **Yi Z, Yokota H, Torii S, Aoki T, Hosaka M, Zhao S, Takata K, Takeuchi T, and Izumi T.** The Rab27a/granuphilin complex regulates the exocytosis of insulin-containing dense-core granules. *Mol Cell Biol* 22: 1858-1867, 2002. **PMID:**11865063
27. **Merrins MJ and Stuenkel EL.** Kinetics of Rab27a-dependent actions on vesicle docking and priming in pancreatic beta-cells. *J Physiol* 586: 5367-5381, 2008. **PMID:**18801842
28. **Figueiredo AC, Wasmeier C, Tarafder AK, Ramalho JS, Baron RA, and Seabra MC.** Rab3GEP is the non-redundant guanine nucleotide exchange factor for Rab27a in melanocytes. *J Biol Chem* 283: 23209-23216, 2008. **PMID:**18559336
29. I**toh T and Fukuda M.** Identification of EPI64 as a GTPase-activating protein specific for Rab27A. *J Biol Chem* 281: 31823-31831, 2006. **PMID:**16923811
30. **Chen Y, Samaraweera P, Sun TT, Kreibich G, and Orlow SJ.** Rab27b association with melanosomes: dominant negative mutants disrupt melanosomal movement. *J Invest Dermatol* 118: 933-940, 2002. **PMID:**12060386
31. **Barral DC, Ramalho JS, Anders R, Hume AN, Knapton HJ, Tolmachova T, Collinson LM, Goulding D, Authi KS, and Seabra MC.** Functional redundancy of Rab27 proteins and the pathogenesis of Griscelli syndrome. *J Clin Invest* 110: 247-257, 2002. **PMID:**12122117
32. **Westbroek W, Lambert J, De Schepper S, Kleta R, Van Den Bossche K, Seabra MC, Huizing M, Mommaas M, and Naeyaert JM.** Rab27b is up-regulated in human Griscelli syndrome type II melanocytes and linked to the actin cytoskeleton via exon F-Myosin Va transcripts. *Pigment Cell Res* 17: 498-505, 2004. **PMID:**15357836
33. **Gomi H, Mori K, Itohara S, and Izumi T.** Rab27b is expressed in a wide range of exocytic cells and involved in the delivery of secretory granules near the plasma membrane. *Mol Biol Cell* 18: 4377-4386, 2007. **PMID:**17761531
34. **Zhao S, Torii S, Yokota-Hashimoto H, Takeuchi T, and Izumi T.** Involvement of Rab27b in the regulated secretion of pituitary hormones. *Endocrinology* 143: 1817-1824, 2002. **PMID:**11956164
35. **Tiwari S, Italiano JE, Jr., Barral DC, Mules EH, Novak EK, Swank RT, Seabra MC, and Shivdasani RA.** A role for Rab27b in NF-E2-dependent pathways of platelet formation. *Blood* 102: 3970-3979, 2003. **PMID:**12907454

36. **Tolmachova T, Abrink M, Futter CE, Authi KS, and Seabra MC.** Rab27b regulates number and secretion of platelet dense granules. *Proc Natl Acad Sci U S A* 104: 5872-5877, 2007. **PMID:**17384153
37. **Shirakawa R, Higashi T, Tabuchi A, Yoshioka A, Nishioka H, Fukuda M, Kita T, and Horiuchi H.** Munc13-4 is a GTP-Rab27-binding protein regulating dense core granule secretion in platelets. *J Biol Chem* 279: 10730-10737, 2004. **PMID:**14699162
38. **Mizuno K, Tolmachova T, Ushakov DS, Romao M, Abrink M, Ferenczi MA, Raposo G, and Seabra MC.** Rab27b regulates mast cell granule dynamics and secretion. *Traffic* 8: 883-892, 2007. **PMID:**17587407
39. **Chen Y, Guo X, Deng FM, Liang FX, Sun W, Ren M, Izumi T, Sabatini DD, Sun TT, and Kreibich G.** Rab27b is associated with fusiform vesicles and may be involved in targeting uroplakins to urothelial apical membranes. *Proc Natl Acad Sci U S A* 100: 14012-14017, 2003. **PMID:**14625374
40. **Bishop BL, Duncan MJ, Song J, Li G, Zaas D, and Abraham SN.** Cyclic AMP-regulated exocytosis of Escherichia coli from infected bladder epithelial cells. *Nat Med* 13: 625-630, 2007. **PMID:**17417648
41. **Song J, Bishop BL, Li G, Grady R, Stapleton A, and Abraham SN.** TLR4-mediated expulsion of bacteria from infected bladder epithelial cells. *Proc Natl Acad Sci U S A* 106: 14966-14971, 2009. **PMID:**19706440
42. **Arimura N, Kimura T, Nakamuta S, Taya S, Funahashi Y, Hattori A, Shimada A, Menager C, Kawabata S, Fujii K, Iwamatsu A, Segal RA, Fukuda M, and Kaibuchi K.** Anterograde transport of TrkB in axons is mediated by direct interaction with Slp1 and Rab27. *Dev Cell* 16: 675-686, 2009. **PMID:**19460344
43. **Johnson JL, Brzezinska AA, Tolmachova T, Munafo DB, Ellis BA, Seabra MC, Hong H, and Catz SD.** Rab27a and Rab27b Regulate Neutrophil Azurophilic Granule Exocytosis and NADPH oxidase Activity by Independent Mechanisms. *Traffic*, 2009. **PMID:**20028487
44. **Ostrowski M, Carmo NB, Krumeich S, Fanget I, Raposo G, Savina A, Moita CF, Schauer K, Hume AN, Freitas RP, Goud B, Benaroch P, Hacohen N, Fukuda M, Desnos C, Seabra MC, Darchen F, Amigorena S, Moita LF, and Thery C.** Rab27a and Rab27b control different steps of the exosome secretion pathway. *Nat Cell Biol* 12: 19-30; sup pp 11-13. **PMID:**19966785
45. **Hendrix A, Maynard D, Pauwels P, Braems G, Denys H, Van den Broecke R, Lambert J, Van Belle S, Cocquyt V, Gespach C, Bracke M, Seabra MC, Gahl WA, De Wever O, and Westbroek W.** Effect of the secretory small GTPase Rab27B on breast cancer growth, invasion, and metastasis. *J Natl Cancer Inst* 102: 866-880. **PMID:**20484105
46. **Chen X, Li C, Izumi T, Ernst SA, Andrews PC, and Williams JA.** Rab27b localizes to zymogen granules and regulates pancreatic acinar exocytosis. *Biochem Biophys Res Commun* 323: 1157-1162, 2004. **PMID:**15451418
47. **Chen X, Walker AK, Strahler JR, Simon ES, Tomanicek-Volk SL, Nelson BB, Hurley MC, Ernst SA, Williams JA, and Andrews PC.** Organellar proteomics: analysis of pancreatic zymogen granule membranes. *Mol Cell Proteomics* 5: 306-312, 2006. **PMID:**16278343
48. **Chen X, Ulintz PJ, Simon ES, Williams JA, and Andrews PC.** Global topology analysis of pancreatic zymogen granule membrane proteins. *Mol Cell Proteomics* 7: 2323-2336, 2008. **PMID:**18682380
49. **Saegusa C, Kanno E, Itohara S, and Fukuda M.** Expression of Rab27B-binding protein Slp1 in pancreatic acinar cells and its involvement in amylase secretion. *Arch Biochem Biophys* 475: 87-92, 2008. **PMID:**18477466
50. **Imai A, Yoshie S, Nashida T, Shimomura H, and Fukuda M.** The small GTPase Rab27B regulates amylase release from rat parotid acinar cells. *J Cell Sci* 117: 1945-1953, 2004. **PMID:**15039459
51. **Imai A, Yoshie S, Nashida T, Fukuda M, and Shimomura H.** Redistribution of small GTP-binding protein, Rab27B, in rat parotid acinar cells after stimulation with isoproterenol. *Eur J Oral Sci* 117: 224-230, 2009. **PMID:**19583748
52. **Imai A, Fukuda M, Yoshie S, Nashida T, and Shimomura H.** Redistribution of Rab27-specific effector Slac2-c, but not Slp4-a, after isoproterenol-stimulation in rat parotid acinar cells. *Arch Oral Biol* 54: 361-368, 2009. **PMID:**19185850
53. **Chavas LM, Torii S, Kamikubo H, Kawasaki M, Ihara K, Kato R, Kataoka M, Izumi T, and Wakatsuki S.** Structure of the small GTPase Rab27b shows an unexpected swapped dimer. *Acta Crystallogr D Biol Crystallogr* 63: 769-779, 2007. **PMID:**17582168
54. **Kukimoto-Niino M, Sakamoto A, Kanno E, Hanawa-Suetsugu K, Terada T, Shirouzu M, Fukuda M, and Yokoyama S.** Structural basis for the exclusive specificity of Slac2-a/melanophilin for the Rab27 GTPases. *Structure* 16: 1478-1490, 2008. **PMID:**18940604
55. **Kondo H, Shirakawa R, Higashi T, Kawato M, Fukuda M, Kita T, and Horiuchi H.** Constitutive GDP/GTP exchange and secretion-dependent GTP hydrolysis activity for Rab27 in platelets. *J Biol Chem* 281: 28657-28665, 2006. **PMID:**16880209