エフェクタータンパク質群による Rab27 取り込みへの 構造的知見

高エネルギー加速器研究機構 物質構造科学研究所 フォトンファクトリー

レオナルド シャバス, 川崎政人, 若槻壮市

高エネルギー加速器研究機構 物質構造科学研究所 構造生物学研究センター 伊原健太郎

Leonard M. G. CHAVAS, Kentaro IHARA, Masato KAWASAKI and Soichi WAKATSUKI:
Structural Insights into Rab27 Recruitment by its Effectors

An increasing number of Rab GTPases associated with partial dysfunction has been linked to several human diseases characterized by a diminution in vesicle transport. Due to its direct implication in human disorders, the Rab27 subfamily is considered as a standard for vesicle docking studies. By which mechanism Rab27 effectors distinguish among the pool of Rab GTPases? What is the underneath machinery rendering the interaction of eleven distinct effectors specific of Rab27 when compared to other Rabs of the secretory pathway? By solving the X-ray structures of Rab27, both in its inactive form and active form bound to the effector protein Slp2-a, attempts have been given to unravel the molecular basis of regulation of the delivering process of vesicles to fusion by the Rab27 subfamily.

小胞輸送の異常によって引き起こされる疾患のいくつかに低分子量 GTPase である Rab の機能不全が関与することが明らかになってきている。とりわけ Rab27 サブファミリーは、その機能不全が疾患に直接かかわることから、小胞輸送における膜のドッキング過程の研究においてモデル分子として広く利用されている。しかしながら、構造化学的な知見は乏しく、数多く存在する Rab の中で、Rab27 のエフェクタータンパク質はどのようなメカニズムで Rab27 を見分けているのか、また、Rab27 のエフェクタータンパク質は 11 種類存在するが、それらの間でどのような違いでもって Rab27 と相互作用を行っているかについては、いまだ不明である。そこで、Rab27 サブファミリーによって制御される輸送小胞の膜融合過程の分子基盤を明らかにするために、Rab 単体、およびエフェクタータンパク質である Slp2-a との複合体の X 線結晶構造解析を行った。

1. Introduction

The integrity of eukaryotic cells depends on the regulation of intracellular membrane trafficking by the Ras superfamily of small GTPases including Ras, Rho/Rac, Rab, Arf/Arl, and Ran proteins. With more than 60 instances in human, members of the ubiquitously expressed Rab/Ypt/Sec4 family act as essential regulators of vesicular transport events such as vesicle budding, cytoskeletal transport, and targeted docking and fusion.¹⁾

Through their specific subcellular localization and nucleotide state, Rab GTPases appear as key elements for the regulation of the vesicular-trafficking machinery, notably by interacting with various effectors at defined place and time (considering the GTP-bound status as a “time-regulator”). A recent push in depicting the molecular basis for the specificity of Rab recognition by their effectors has lead

to the structure determinations of numerous Rab:effector complexes.²⁾⁻¹¹⁾ Among Rabs, the distinct subfamily of so-called “secretory Rabs” is responsible for the transport of lysosome-related organelles, also known as secretory lysosomes, during their exocytosis.¹²⁾ Well-studied members of secretory Rabs, Rab27a and Rab27b have been associated with multiple phenotypes that show deleterious effects on vesicle exocytosis.¹³⁾ Notably, Griscelli syndrome 2 (GS2; OMIM 214450) patients display mutations in the *RAB27A* gene, *ashen* in mouse, representing the first direct association of a Rab GTPase with human diseases.¹⁴⁾ Other syndromes partially linked to Rab27 loss of function include choroideremia, and the Hermanski-Pudlak syndrome.¹³⁾

Due to the characteristic phenotypes emerging from its dysfunction, Rab27 is considered a good model for the study of vesicle transport and docking, and has been intensively analyzed. Thus, Rab27a and Rab27b were shown to control

the secretion in endocrine/exocrine tissues and melanocytes by recruiting cell-type specific effector proteins,^{15),16)} with currently eleven different effectors identified for Rab27. Two of the effectors, Melanophilin and Slp2-a, are responsible for the proper targeting of melanosome vesicles in melanocyte cells.¹²⁾ Although the effectors involved in the secretory pathway are able to form complexes with most of the secretory Rabs, they present higher affinities for Rab27 isoforms.¹⁷⁾ Additionally, some differences were also observed among the effectors for their response towards Rab27, which lead to their grouping as high and low specificity effectors. Prior to fully understand Rab27-mediated vesicle docking events, it is necessary to clarify the specificities and differences behind the recruitment of effectors by the GTPase.

In a massive structure determination of eleven distinct Rabs, Eathiraj et al. highlighted the importance of positive and negative determinants that mold in Rabs complementary interacting surfaces for specific effector recognition.⁵⁾ Similarly, the strength of Rab recruitment by various effectors might be altered by the degree of complementarities between Rab and effector interacting surfaces. Although the importance of Rab surfaces could be confirmed based on structural data, the modulation of divers effector surfaces recognizing a single Rab could not be clearly observed yet. Recently, the structure of Rab27 alone and in complex with two distinct effectors could be determined.^{9),10),18)} With these data in hands, and by comparison with the existing Rab: effector complex structures (i.e. Rab3:Rabphilin3-a), it has been possible to elucidate the recruitment mechanism of Rab27 by its effectors, allowing to understand more deeply the vesicle docking process it is involved in.

This review is a *memoire* of Rab27 structural characterization. It regroups data on its crystallization and structure determination, both in its inactive GDP-bound form and active GTP-analog bound form in complex with the effector protein Slp2-a.

2. Material and methods

2.1 Cloning, expression, purification and crystallization

The C-terminal hypervariable regions of GTPase-inactive mouse Rab27a and Rab27b Q78L mutants were shortened during cloning, with eventually cysteine mutations C123S and C188S. The human Slp2-a was limited to its Rab27-binding domain (RBD27, residues [10-62]). All constructs were independently expressed as GST-tagged recombinant proteins. Rab27 samples were purified by affinity and size exclusion chromatographies. Nucleotide exchange was performed on the resin. Complex formation was performed

on GST-Slp2-a loaded resins by addition of Rab27 in excess amount. After removal of GST, the Rab27:Slp2-a complex was purified by size-exclusion chromatography. Pure protein fractions were pooled independently, and concentrated to 10 mg/ml. The purity of the samples was greater than 95 % based on SDS-PAGE analysis. More than 10,000 independent crystallization conditions were screened for the GTPases alone. No protein crystal could be observed for Rab27a isoforms. Rab27b crystallized in three different space groups. Crystals of full-length Rab27b [1-218] diffracted to 8 Å resolution. C-terminal truncations enhanced the resolution to about 3 Å. Hexagonal crystals (space group $P6_522$, unit-cell parameters $a = b = 66.1$, $c = 380$ Å) of Rab27b [1-193] grew in few days at 293 K from PEG10K in the presence of 5 mM DTT, at pH 7.5. Monoclinic and orthorhombic crystals ($C2$, $a = 170.6$, $b = 63.4$, $c = 80.9$ Å, $\beta = 98.4^\circ$; $P2_12_12_1$, $a = 55.0$, $b = 64.8$, $c = 153.3$ Å) of Rab27b [1-215] and [1-198] appeared after several months from a solution containing MPD, and either $CaCl_2$ or Na cacodylate, at pH 7.0 and 5.5, respectively. The complex between Rab27a [1-193] triple mutant Q78L C123S C188S and Slp2-a [10-62] crystallized at 289 K. Orthorhombic crystals appeared in few days from Na citrate at pH 6.5.

2.2 Data collection, structure determination and refinement

All diffraction data were indexed, integrated, scaled and merged using *HKL-2000*. Crystals were flash-cooled in a 100 K dry N_2 stream. Single wavelength anomalous dispersion (SAD) diffraction data at 3.2 Å resolution from a $P6_522$ crystal of SeMet-labelled Rab27b·GDP were recorded at a wavelength of 0.9789 Å on PF BL6A. The program *SOLVE* located six Se atoms for two Rab27b molecules in the asymmetric unit (ASU). Diffraction data from a $C2$ crystal were collected at 2.8 Å resolution on BL5A. Four Rab27b·GDP- Ca^{2+} per ASU were identified by molecular replacement (MR) method using one Rab27b core domain from the $P6_522$ crystal structure as a search model. The $P2_12_12_1$ crystals diffracted to 2.8 Å resolution at BL6A. The structure was solved by MR using one monomer from the $C2$ crystal structure. Two molecules of Rab27b·GDP- Mg^{2+} are in the ASU. Rab27a:Slp2-a crystal data were collected on BL5A at 1.8 Å resolution. Two heterodimeric complexes are in the ASU. A self-rotation peak at $\kappa = 180^\circ$ supported a two-fold NCS assignment. Phases were determined by MR, with one Rab27b core domain coupled to the switch elements of Rab3 as the search model (PDB codes 2if0 and 1zbd, respectively). Initial models were built using the program *ARP/WARP*, followed by iterative cycles of rebuilding with

Table 1 Summary of data collection and refinement statistics.

Molecule	Rab27b·GDP	Rab27b·GDP	Rab27b·GDP	Rab27a·GDPNP : Slp2-a RBD27
PDB	2iey	2iez	2if0	3bc1
DATA COLLECTION STATISTICS				
Space group	<i>P</i> 6 ₅ 22	<i>C</i> 2	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁
Temperature (K)	100	100	100	100
X-ray source	PF BL6A	PF BL5A	PF BL6A	PF BL5A
Detector	ADSC Q4R	ADSC Q315r	ADSC Q4R	ADSC Q315r
Unit-cell parameters (Å, °)	<i>a</i> = 66.06, <i>c</i> = 379.99	<i>a</i> = 170.55, <i>b</i> = 63.39, <i>c</i> = 80.93, γ = 98.44	<i>a</i> = 54.96, <i>b</i> = 64.76, <i>c</i> = 153.33	<i>a</i> = 53.51, <i>b</i> = 77.78, <i>c</i> = 115.01
Wavelength (Å)	0.9789	1.0000	1.0000	1.0000
Resolution (Å)	63.4–3.2	84.2–2.8	40.1–2.8	30.3–1.8
Reflections	246,530	58,126	93,323	112,804
Unique reflections	9,175	11,277	14,413	45,327
<i>R</i> _{merge} (%) ¹	11.1 (69.3)	10.5 (27.1)	10.9 (41.8)	9.3 (63.4)
Completeness (%)	99.8 (100.0)	98.1 (93.8)	99.7 (97.4)	95.7 (98.6)
$\langle I \rangle / \langle \sigma(I) \rangle$	10.8 (8.5)	8.2 (3.9)	13.1 (3.3)	6.5 (1.3)
PHASING STATISTICS				
FOM	0.31	—	—	—
FOM after <i>RESOLVE</i>	0.69	—	—	—
REFINEMENT STATISTICS				
Resolution (Å)	3.2	2.8	2.8	1.8
<i>R</i> factor (%) ²	28.9	26.2	25.9	19.9
<i>R</i> _{free} (%) ²	34.6	36.3	31.5	24.5
R.m.s.d. bond lengths (Å)	0.009	0.008	0.008	0.007
R.m.s.d. bond angles (°)	1.181	1.189	1.067	1.054
Average <i>B</i> factors (Å ²)/No. of atoms				
Protein non-H atoms	51.0/2,671	56.8/5,600	41.8/2,849	20.9/3,773
Water molecules	35.8/11	39.5/38	24.3/14	30.2/351
Ligand non-H atoms	GDP	GDP-Ca ²⁺	GDP-Mg ²⁺	GDPNP-Mg ²⁺
	39.8/56	45.2/116	31.7/58	12.4/66
Φ/Ψ angles (%)				
Most favoured	81.7	86.7	90.8	94.3
Additionally allowed	16.6	12.8	8.9	5.7
Generously allowed	1.7	0.5	0.3	—

¹ $R_{\text{merge}} = \sum_j \sum_i |I_j(h) - \langle I(h) \rangle| / \sum_j \sum_i I_j(h)$, where $I_j(h)$ is the *j*th measurement of reflections indices *h* and $\langle I(h) \rangle$ is the mean intensity.

² R factor = $\sum_h ||F_o(h)| - |F_c(h)|| / \sum_h |F_o(h)|$; R_{free} was calculated using 5% of data excluded from refinement.

COOT, coupled to refinements with *REFMAC5*. Data statistics are summarized in Table 1.

3. Results

3.1 Structure determinations

During this work, four crystal structures of Rab27 were unraveled, including three structures of Rab27b·GDP and one structure of Rab27a·GDPNP : Slp2-a complex. The initial phases of Rab27b·GDP crystals could not be obtained by MR despite the high sequence similarity and conserved folding among Rabs. As a consequence, the SAD method was used to determine the structure of Rab27b·GDP from *P*6₅22 crystals. The ASU contains one homodimer of Rab27b. One monomer excluding the switch elements from the *P*6₅22 structure was used for MR on the monoclinic crystal data. Two dimers are present in the ASU. These coordinates

were used for MR phasing of the orthorhombic structure of Rab27b·GDP. The *P*2₁2₁2₁ lattice contains one dimer per ASU. The Rab27a·GDPNP:Slp2-a complex structure was determined using a model of a Rab27b::Rab3a chimera for MR. The ASU accommodates two complexes. Overall, the four structures show good statistics and stereochemistry (Table 1). However, the low quality of the data for the *P*6₅22 and *C*2 crystals and the high *B* factors result in elevated values of the *R*_{free}.

3.2 Rab27a/b and Slp2-a structures

A domain-swapped dimer is created by a protrusion of the switch elements of inactive Rab27b·GDP (Fig.1a). Although the core domain of Rab27b superposes well with other Rab structures (~1.40 Å C α rmsd), this arrangement is the first to reveal such an extended form. In contrast, the structure of active Rab27a·GDPNP exhibits a typical

Fig.1 Crystal structure of Rab27 and Slp2-a. Ribbon diagram of (a) Rab27b·GDP-Mg²⁺, (b) Rab27a·GDPNP-Mg²⁺, and (c) Slp2-a. Secondary structure elements are labeled correspondingly. Switch elements and RBD27 subdomains are indicated. Nucleotides are represented as ball-and-sticks model.

Fig.2 Rab27b·GDP domain swapping. Ribbon diagram of the domain swapped Rab27b·GDP, together with molecular surface representation of one monomer in the background. The inlet represents a zoomed-in view of the hydrophobic interface between both molecules of the dimer.

GTPase globular fold (Fig.1b). Surface areas of 3298, 3064 and 2956 Å² are buried by the domain-swapped interfaces extracted from the P₆₅₂₂, C2 and P₂₁₂₁₂₁ lattices, respectively. Swapping occurs at the interswitch region, with β2 and β3 strands that enter the swapped molecule. The α2 helix hydrophobic side packs against an intermolecular β-sheet, with hydrophobic L84 and F88 that shape a groove to accept I44 of β2 strand (Fig.2). Rab27a·GDPNP and Rab27b·GDP core domains are structurally similar (~1.0 Å Cα rmsd). The α3 helix shifts by ~20°, resulting in a flipped Y122 as observed for Rab27b without the C123-C188 disulfide bridge.¹⁸⁾ The fact that C123S and C188S

Fig.3 Rab27a·GDPNP:Slp2-a complex. Ribbon diagram of Rab27a in complex with Slp2-a, together with molecular surface representation of Slp2-a in the background. The view is rotated 180° when compared with Fig.1. Both inlets are zoomed-in views of the specific interactions through RBD27-1 (lower) and RBD27-2 (upper) regions.

mutations enhanced complex formation with Slp2-a, whereas Y122A mutation abolished it, corroborates well with Y122 being essential for Slp2-a recognition. Additionally, Rab27a switch elements fold back near the core domain in the GTPase active conformation, in order to coordinate GDPNP γ-phosphate. Slp2-a RBD27 folds as an elongated hook-like structure with a long N-terminal α helix (RBD27-1), and two short helices (RBD27-2) with higher *B* factors (~35 Å²) (Fig.1c).

3.3 Rab motifs and effector recognition

Rab-family (RabF) and subfamily (RabSF) motifs enable the recognition of distinct effectors.¹⁹⁾ In Rab27b·GDP, RabF1-4 are engaged in dimerization, RabF5 buried in the protein, and RabSF1-4 exposed to the solvent. RabSF1, 3 and 4 have elevated *B* factors, whereas they form part of the complex interface with Slp2-a, together with RabF1-4. Rab27a·GDPNP and Slp2-a share an accessible surface of 1970 Å². Slp2-a RBD27-1 packs against interswitch and switch II (RabF1-3), centered at the invariant hydrophobic made of Rab27 F46, W73, and F88. The three residues form an extended hydrophobic cluster that accommodates bulky residues of Slp2-a. The conserved structural element (S/T) (G/L)xW(F/Y)2 of Slp2-a (SGQWFY) recognizes Rab27a RabF4, RabSF4 and RabSF3 motifs via van der Waals interactions between W53 and F54, and Rab27 M93, M185, and Y122 (Fig.3).

4. Discussion

By binding Rab27a on the surface of melanosomes and secretory granules through an N-terminal RBD27 domain, Slp2-a takes part in the transport of these organelles to the cell periphery.¹²⁾ In the RBD27 of Slp2-a, RBD27-1 and RBD27-2 motifs are linked directly without an inserted zinc-binding domain. While making the present complex with Rab27a·GDPNP, Slp2-a RBD27 adopts an overall helical fold, composed of $\alpha 1$ (RBD27-1) and $\alpha 2/3$ (RBD27-2) helices arranged in a hook-like structure. As a general observation, the GTPase-binding regions of Rab effectors are mostly composed of α helices that are aligned along the switch region of GTP-bound activated Rabs.²⁰⁾ Accordingly, an extended interface with the switch II and interswitch elements of Rab27a is generated by polar ($\sim 60\%$) and hydrophobic ($\sim 25\%$) residues within Slp2-a $\alpha 1$ helix (RBD27-1). Supported by an armful of published data, the invariant Rab27 hydrophobic triad, composed of F46, W73, and F88, appears to be essential for effector recognition. The missense mutation W73G in *RAB27A*, in particular, has been associated with GS.¹⁴⁾ In the structure of the Rab27a:Slp2-a complex, the side chain of W73 stabilizes the bulky side chains of Rab27 F46 and F88 as they recognize Slp2-a V18 of RBD27-1, a conserved residue among RBD27-containing effectors.

Nearly all the Slp2-a RBD27-1 residues involved in the recognition of Rab27a·GDPNP in the present complex structure have been shown experimentally to be necessary for the proper recruitment of Rab27.^{9),10)} Interestingly, most of these residues are conserved among all RBD27-containing effectors, which agrees with a conventional recognition pattern of these effectors for Rab27. Auxiliary contact surfaces at the periphery of the Rab27 switch elements further interact with Slp2-a RBD27-2, in particular with the characteristic (S/T)(G/L)xW(F/Y)2 motif. The spatial conformation of the motif creates a stacking interaction between Slp2-a F54 and Rab27 Y122. The different orientation of Y122 when compared with the corresponding W125 of Rab3, or S110 of Rab8, other members of the secretory Rab subfamily, might be at the origin of the recognition specificity of Slp2-a (or other RBD27-containing effectors such as Melanophilin) towards Rab27. In addition, because the residues in the RBD27-1/2 motifs are highly conserved, the observed differences among the effectors in regards to their singularity for Rab27 recruitment could be ascribed to the relative positions of RBD27-1 and RBD27-2.

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プロフィール

レオナルド シャバス Leonard M. G. CHAVAS
高エネルギー加速器研究機構 物質構造科学研究所
フォトンファクトリー

Photon Factory, Institute of Materials Structure
Science, KEK

〒305-0801 茨城県つくば市大穂 1-1

1-1 Oho, Tsukuba, Ibaraki 305-0801, Japan

e-mail: leonard.chavas@kek.jp

専門分野：構造生物学, タンパク質結晶学
現在の研究テーマ：放射光 X 線ビームラインを利用した構造生物学

伊原健太郎 Kentaro IHARA
高エネルギー加速器研究機構 物質構造科学研究所
構造生物学研究センター
Structural Biology Research Center, Institute of
Materials Structure Science, KEK
〒305-0801 茨城県つくば市大穂 1-1
1-1 Oho, Tsukuba, Ibaraki 305-0801, Japan
e-mail: kentaro.ihara@kek.jp
専門分野：タンパク質などの結晶構造解析
現在の研究テーマ：低分子量 GTPase などの結晶
構造解析

川崎政人 Masato KAWASAKI
高エネルギー加速器研究機構 物質構造科学研究所
フォトンファクトリー
Photon Factory, Institute of Materials Structure
Science, KEK
〒305-0801 茨城県つくば市大穂 1-1
1-1 Oho, Tsukuba, Ibaraki 305-0801, Japan
e-mail: masato.kawasaki@kek.jp
専門分野：構造生物学
現在の研究テーマ：細胞内輸送にかかわるタンパ
ク質の結晶構造解析

若槻壮市 Soichi WAKATSUKI
高エネルギー加速器研究機構 物質構造科学研究所
フォトンファクトリー
Photon Factory, Institute of Materials Structure
Science, KEK
〒305-0801 茨城県つくば市大穂 1-1
1-1 Oho, Tsukuba, Ibaraki 305-0801, Japan
e-mail: soichi.wakatsuki@kek.jp
専門分野：放射光 X 線ビームラインとそれを利用
した構造生物学, 特にタンパク質結晶構造解析
現在の研究テーマ：細胞内タンパク質輸送系・糖
鎖修飾系の構造生物学