GAT (GGA and Tom1) Domain Responsible for Ubiquitin Binding and Ubiquitination*

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GGAs (Golgi-localizing, γ-adaptin ear domain homology, ADP-ribosylation factor (ARF)-binding proteins) are a family of monomeric adaptor proteins involved in membrane trafficking from the trans-Golgi network to endosomes. The GAT (GGA and Tom1) domains of GGAs have previously been shown to interact with GTP-bound ARF and to be crucial for membrane recruitment of GGAs. Here we show that the C-terminal subdomain of the GAT domain, which is distinct from the N-terminal GAT subdomain responsible for ARF binding, can bind ubiquitin. The binding is mediated by interactions between residues on one side of the αβ helix of the GAT domain and those on the so-called Ile-44 surface patch of ubiquitin. The binding of the GAT domain to ubiquitin can be enhanced by the presence of a GTP-bound form of ARF. Furthermore, GGA itself is ubiquitinated in a manner dependent on the GAT-ubiquitin interaction. These results delineate the molecular basis for the interaction between ubiquitin and GAT and suggest that GGA-mediated trafficking is regulated by the ubiquitin system as endosomal trafficking mediated by other ubiquitin-binding proteins.

In eukaryotic cells, monoubiquitination of proteins plays a crucial role in membrane trafficking (1–4). In yeast, ubiquitinated transmembrane proteins are sorted into luminal vesicles of the multivesicular body (MVB)1 and/or vacuole along both the endocytic and biosynthetic pathways. In mammalian cells, ubiquitin-dependent transport to the MVB/lysosome has so far been demonstrated only along the endocytic pathway, such as that of the epidermal growth factor receptor. Cells transmit the ubiquitination signals through proteins containing conserved ubiquitin-binding modules including the UBA (ubiquitin-associated domain), CUE (coupling of ubiquitin to endoplasmic reticulum degradation domain), UIU (ubiquitin-interacting motif), UEV (ubiquitin E2 variant domain), and NZF (Npl4 zinc finger domain) (see Ref. 4 and references therein). One or combinations of these domains are often found in proteins implicated in endocytic processes, such as MVB pathway.

GGAs (Golgi-localizing, γ-adaptin ear domain homology, ARF-binding proteins) are a family of monomeric adaptor proteins that regulates clathrin-mediated trafficking of cargo proteins from the trans-Golgi network (TGN) to endosomes (5, 6). The GGA molecule is composed of four functional domains (Fig. 1). 1) The N-terminal VHS (Vps27p/Hrs/Stam) domain recognizes the acidic amino acid cluster-dileucine motifs found in the cytoplasmic domains of TGN-sorting receptors such as mannose 6-phosphate receptors (7–10). 2) The GAT (GGA and Tom1) domain interacts with a GTP-bound form of the small GTPase ADP-ribosylation factor (ARF) and is responsible for association of GGAs with TGN membranes (11–14). 3) The proline-rich hinge region mediates recruitment of clathrin (15). 4) The C-terminal γ-adaptin ear homology domain interacts with various accessory proteins (see Ref. 6 and references therein).

The GAT domain is conserved in GGAs and Tom1 (target of Myb) 1). Tom1 was originally identified as a protein whose expression was induced by v-Myb (15). Although Tom1 also contains the VHS domain (12), its function is currently unknown. Neither does its VHS domain bind to the acidic amino acid cluster-dileucine motif (8, 10) nor does its GAT domain bind to ARF.2 In the course of searching for binding partners of Tom1, we have found that the GAT domains interact with ubiquitin. We here show that the GGA-GAT domain binds ARF and ubiquitin through distinct subdomains and its binding to active ARF enhances the efficiency of the ubiquitin binding. Furthermore, we show that GGA itself is ubiquitinated in a manner dependent on the GAT-ubiquitin interaction. Our results suggest that GGA might regulate membrane trafficking in a ubiquitin-dependent manner.

EXPERIMENTAL PROCEDURES

Plasmid Construction—Vectors for domains of human GGA1 (VHS+GAT (residues 1–327); VHS+GAT+Tom1; and C-Ub-AP).**

This paper is available on line at http://www.jbc.org/
shown in Fig. 3

[59x546]A addition of 1

[59x750]fusion proteins (H11011 Novagen). To examine GAT interaction with ubiquitinated proteins, down with GST-Ub as above and detected by anti-T7 tag antibody (H9262 follows. A mixture of multi-ubiquitin chain (2

[59x156]/H9262 products) and varying amounts of purified recombinant ARF1 subjected to immunoblotting with anti-GGA3 antibody (BD

[59x201]°

[59x925]/H9251 temperature in buffer A (25 mM Hepes, pH 7.4, 125 mM KOAc, 2.5 mM MgOAc, 5 mM EDTA, 1 mM dithiothreitol) containing 0.1% bovine serum albumin and 0.1% Triton X-100. The beads were then pelleted and washed three times with buffer B containing 7 mM MgCl₂ and 10 μM GDP or GTP-γS. Proteins associated with the beads were subjected to immunoblotting with monoclonal anti-ubiquitin antibody P4D1 (Santa Cruz Biotechnology).

FIG. 1. Schematic diagram of the domain organization of human GGA3L. Regions of GGA3 domain constructs used in this study are indicated. α0, α1, α2, and α3 correspond to the α-helical regions shown in Fig. 3A.

RESULTS

GAT Domains Interact with Ubiquitin—A two-hybrid screening of a human brain cDNA library using the VHS+GAT domain of human Tom1 as bait yielded 44 positive clones. Among them, six encoded ubiquitin precursors containing one to six tandem ubiquitin units. Subsequent two-hybrid and pull-down analyses revealed that the GAT domain is responsible for the interaction with ubiquitin.³

To examine whether the ubiquitin binding is a general feature of the GAT domains, we performed a similar experiment with GGA3. As shown in Fig. 2A, GST fusion proteins containing but not lacking the GAT domain of GGA1 was bound to Ub-agarose beads. As shown in Fig. 2B, the GAT domains of GGA1 and GGA3, but not that of GGA2, was bound to Ub-agarose beads. These data demonstrate that the GAT domains of GGA1 and GGA3 directly interact with ubiquitin. Because the GGA3-GAT binding to ubiquitin was relatively efficient among the GGA-GAT domains examined, we thereafter focused mainly on the GGA3-GAT domain.

We then examined the binding ability of the GAT domains to ubiquitinated proteins. Rat liver cytosol was pulled down with the GST-GAT domains pre-bound to glutathione-Sepharose beads and subjected to immunoblotting using the monoclonal antibody FK2, which recognizes monoubiquitinated and polyubiquitinated proteins but not free ubiquitin (20, 21). As shown in Fig. 2C, the GAT domains of GGA1 (lane 9) and GGA3 (lane 5) but not that of GGA2 (lane 10) could bind ubiquitinated proteins, being in line with the data in Fig. 2B. The VHS domain (lane 4) or the C-terminal region (lane 3) did not bind ubiquitinated proteins. It is notable that compared with the band pattern of ubiquitinated proteins in the original cytosol (lane 11), the GAT domains appeared to bind selected ubiquitin-conjugated proteins (lanes 5 and 9). In a reciprocal experiment, GST-Ub could pull down endogenous GGA3 from both cytosolic and membrane-bound fractions (Fig. 2D).

In addition, the expression of GGA3 at moderate to high levels in cells caused accumulation of ubiquitinated proteins detected with the FK2 antibody in the Golgi region (Fig. 2E, a and a’), indicating that GGA3 binds ubiquitinated proteins in the cell. The accumulation of ubiquitinated proteins was specific for GGA3, because such accumulation was not observed in cells expressing GGA2 at high levels (data not shown). The GAT-ubiquitin interaction contributed significantly to the GGA3-dependent accumulation of ubiquitinated proteins because 60% of GGA3-overexpressing cells (n = 50) accumulated ubiquitinated proteins, whereas 34% of cells (n = 50) overexpressing a GGA3

³. Y. Kato, Y. Shiba, H. Takatsu, and K. Nakayama, submitted for publication.
subdomains N-GAT and C-GAT, respectively (Fig. 3 and more importantly that ARF and ubiquitin bind distinct a three-helix bundle is responsible for the ubiquitin binding 6

b

or its L280R mutant (b) were double-stained with anti-HA antibody (a and b) and the FK2 antibody (a' and b').

ARF and Ubiquitin Bind Distinct GAT Subdomains—We next attempted to delineate the region of the GGA3-GAT domain required for ubiquitin binding. Recent x-ray crystallographic studies of the GGA1-GAT domain from our and other laboratories have revealed that it possesses an α-helical fold comprising two subdomains (see Fig. 3, A and D) (22–25). The N-GAT or hook subdomain is a helix-loop-helix structure composed of the first short helix α0 (the helix numbering is according to Ref. 24) and the N-terminal half of the second long helix α1 and is responsible for ARF binding (22, 24, 25). The C-GAT subdomain constitutes a helix bundle composed of the C-terminal half of α1, α2, and α3 (22–25). Surprisingly, the deletion of the N-GAT subdomain significantly enhanced the binding efficiency to ubiquitinated proteins (compare lane 5 for GAT with lane 7 for C-GAT in Fig. 2C). Deletion of the entire α1-helix abolished the binding to ubiquitinated proteins (lane 8), which presumably makes the three-helix bundle unstable. In addition, deletion of the entire α3-helix abolished the binding (lane 6). These data indicate that the C-GAT subdomain comprising a three-helix bundle is responsible for the ubiquitin binding and more importantly that ARF and ubiquitin bind distinct subdomains N-GAT and C-GAT, respectively (Fig. 3D).

To further define the interface of the GAT domain with ubiquitin, we subjected the C-GAT subdomain to a reverse two-hybrid screening with ubiquitin to identify C-GAT mutants defective in ubiquitin binding. The screening identified six missense mutants (L247P, L262S, L276S, L280R, D284G, and Y293H) (Fig. 3A). Among these mutations, L247P, L262S, and Y293H seemed to disrupt the packing of the helix bundle deduced from the structure of the GGA1-GAT domain (data not shown). On the other hand, the side chains of Leu-276, Leu-280, and Asp-284 appeared exposed on one side of α3 and could be responsible for protein-protein interactions (see Fig. 3B).

Ubiquitin Binds GAT through Its Ile-44 Patch—On ubiquitin, two surface patches have been shown to participate in binding to the proteasome, UIM, UBA, and CUE domains and in intracellular trafficking, one patch including Ile-44 and the other including Phe-4 (1, 4, 26–29). To examine which patch is responsible for the GAT binding, His6+T7-tagged GGA3-GAT was incubated with wild type Ub, Ub(F4A), or Ub(I44A) fused to GST, pulled down with glutathione-Sepharose, and subjected to immunoblotting with anti-T7 tag antibody. The experiment revealed that the GAT-ubiquitin interaction requires Ile-44 but not Phe-4 on the ubiquitin surface (Fig. 4A).

Mode of GAT-Ubiquitin Interaction—On the basis of the above mutational data and three-dimensional structures of GGA1-GAT and ubiquitin, we constructed the most plausible model for the interaction between GGA3-GAT and ubiquitin.
In this model, Asp-284 interacts with Arg-42\(\text{U}\) (the superscript \(\text{U}\) denotes a residue of ubiquitin), Leu-276 with both Leu-8\(\text{U}\) and Val-70\(\text{U}\), and Leu-280 with both Ile-44\(\text{U}\) and Val-70\(\text{U}\). To address this model, we constructed additional ubiquitin mutants and examined their interactions with GGA3-GAT. As expected, L8A, R42A, and V70A mutations of ubiquitin abolished the GAT binding (Fig. 4B). These data make it most likely that the GAT domain interacts with ubiquitin in a manner presented in this model (Fig. 3, B and C).

**ARF Binding to GAT Affects Ubiquitin Binding**—The data presented here along with the previous data (13, 14) show that the GAT domain can interact with ARF and ubiquitin through distinct subdomains, N-GAT and C-GAT, respectively. The interface between GAT and ARF and that between GAT and ubiquitin are sterically separated (Fig. 3D). Furthermore, GGA3-GAT mutants defective in ubiquitin binding can bind ARF-GTP\(\text{S}\) and a GGA1-GAT mutant defective in ARF binding can bind ubiquitin (data not shown). However, the enhancement of ubiquitin binding by deleting the N-GAT subdomain (compare lanes 5 and 7 in Fig. 2C) suggests a possibility that some conformational change in the N-GAT subdomain may affect ubiquitin binding to the C-GAT subdomain. To address this possibility, multi-ubiquitin chains were pulled down with the GGA3 VHS\(\text{S}\)/H11001-GAT domain in the presence of increasing concentrations of purified ARF1-GDP or ARF1-GTP\(\text{S}\) (in this experiment, we used VHS\(\text{S}\)/H11001 in place of GAT because the former bound ARF more strongly than the latter) and subjected to immunoblotting using the monoclonal anti-ubiquitin antibody P4D1. As shown in Fig. 5, more ubiquitin chain was

![Fig. 3. Models for interaction between the GAT domain and ubiquitin. A, alignment of amino acid sequences of the GAT domains from human GGAs. Residues conserved in all GGAs are shown in blue. Residues involved in packing of the helix bundle (Leu-247, Leu-262, and Tyr-293) and those involved in interaction with ubiquitin (Leu-276, Leu-280, and Asp-284) are indicated by black and red arrowheads, respectively. Boxes above the sequences depict \(\alpha\)-helical regions. The helix numbering is according to Ref. 24. B, ribbon diagrams of a model for interaction mode between GGA3-GAT and ubiquitin deduced from experimental data. C, schematic representation of the GAT-ubiquitin interaction shown in B. D, a model of the interactions of the GAT domain with ARF and ubiquitin.

![Fig. 4. Effects of mutations of residues in the GGA3-GAT domain and ubiquitin on their interaction. A, wild type (WT) GGA3-GAT domain or its mutant fused to GST was pulled down with Ub- or protein A (pro A)-agarose and subjected to immunoblotting using anti-GST antibody. On input lanes, 2.5% of input samples were loaded. B, His\(\text{S}\)/H11001-T7-tagged wild type GGA3-GAT or its mutant was incubated with GST-Ub pre-bound to glutathione-Sepharose and subjected to immunoblotting using anti-T7-tag antibody. On input lanes, 2.5% of input samples were loaded.](https://doi.org/10.1074/jbc.R106.700003)

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pulled down with the GGA3-VHS+GAT domain as the increasing concentration of ARF in the presence of GTPγS. In contrast, the ARF-dependent increase in the ubiquitin binding was marginal in the presence of GDP. The results suggest that the binding of ARF to the N-GAT subdomain might allosterically affect the ubiquitin binding to the C-GAT subdomain.

**GGA Ubiquitination Depends on GAT-Ubiquitin Interaction**

A number of, albeit not all, proteins that bind ubiquitin have been reported to undergo monoubiquitination (30–34), although the regulatory mechanism underlying the coupling of ubiquitin binding and ubiquitination is currently uncertain. To examine whether this was also the case with GGA, lysates from cells transfected with expression vectors for various His6/FLAG-tagged GGA3 constructs together with that for HA-ubiquitin were precipitated with Ni2+-nitrilotriacetic-agarose beads under denaturing conditions and subjected to immunoblotting with anti-FLAG antibody to confirm the efficiencies of protein expression and precipitation. As shown in Fig. 6A, full-length GGA3 and constructs containing the GAT domain were efficiently ubiquitinated in the cells. The results indicate that the ubiquitination occurs within the GAT domain. In addition, the difference between the bands detected with anti-FLAG and anti-HA antibodies in size (~8 kDa) indicates monoubiquitination at least in the cases of the GAT and VHS+GAT constructs, although faint bands suggesting diubiquitination or triubiquitination are also detectable. The VHS domain was slightly ubiquitinated, although we did not address its significance further. The C-terminal construct that includes the hinge region and the γ-adaptin ear homology domain was not ubiquitinated at all.

We then examined whether the GAT-ubiquitin interaction is prerequisite for ubiquitination. Unlike wild type full-length GGA3, ubiquitination of the L280R and D284G mutants was extremely reduced in the transfected cells (Fig. 6, B and C), demonstrating that prior ubiquitin binding to the GAT domain makes a major contribution to the GGA ubiquitination.

**DISCUSSION**

The GAT domain has attracted our attention by its role in ARF binding and concomitant recruitment onto TGN membranes of GGAs. In this study, we have found that the GAT domains can interact with ubiquitin through the C-GAT subdomain, which is distinct from the N-GAT subdomain responsible for ARF binding. However, the GAT-ubiquitin interaction can be enhanced by ARF-GTP. Furthermore, ubiquitination of GGA3 occurs in a manner dependent on the GAT-ubiquitin interaction.
N-terminal domains of syntaxin-1a and its relatives (22–25) and is implicated in interaction with Rabaptin-5 (25, 35). By analogy with SNARE-motif binding sites of the syntaxin N-terminal domains, a hydrophobic patch formed by residues of helices α2 and α3 of GAT was proposed to constitute a protein-protein interaction site (23). We have shown that together with Asp-284, the hydrophobic patch of GGA3-GAT indeed participates in ubiquitin binding.

On the other hand, we have also delineated the GAT-binding interface of ubiquitin by mutational experiments, although our attempts to make a co-crystal of GAT and ubiquitin have been unsuccessful so far. Similar to interactions with other ubiquitin-binding modules, the Ile-44 surface patch of ubiquitin including Leu-8, Ile-44, Arg-42, and Val-70 mediates the GAT interaction. While this study was in progress, NMR and x-ray analyses revealed structural bases for ubiquitin interactions with CUE, NZF, and UIM (36–39). All of the studies pointed to the importance of the Ile-44 hydrophobic patch in these interactions. The engagement of the overlapping ubiquitin surface by multiple ubiquitin-binding modules including CUE, UIM, NZF, and GAT has important implications in membrane trafficking. For example, these ubiquitin-binding proteins might sequentially interact with the same ubiquitinated cargo protein along the transport pathway. Ubiquitination of these ubiquitin-binding proteins themselves might contribute to the sequential interactions.

In contrast to the GAT domains of GGA1, GGA3, and Tom1, we failed to show ubiquitin binding of GGA2-GAT. In the case of other ubiquitin-binding modules, all of the family members cannot interact with ubiquitin (31). However, the residues that we have shown to be essential for ubiquitin binding are identical in all human GGAs. One possible explanation for the apparent discrepancy is that residues other than those we have determined in GGA3-GAT are also essential for ubiquitin interaction but are different from corresponding residues of GGA2-GAT. Alternatively, the GAT domain of GGA2 might be somewhat different from those of GGA3 and GGA1 in the overall structure and might be unable to accept ubiquitin.

Structural determination of GGA2-GAT and a complex between GGA3-GAT and ubiquitin will help to discriminate between these possibilities.

Another key finding in this study is that ubiquitinated proteins accumulate in the Golgi region in GGA3-overexpressing cells, suggesting an implication of the ubiquitin system in the biosynthetic pathway. In mammalian cells, there has been no evidence for the existence of biosynthetic pathway regulated by the ubiquitin system in contrast to the endocytic pathway, whereas in yeast, some biosynthetic cargos are sorted into MVb luminal vesicles in a ubiquitin-dependent manner (reviewed in Ref. 2) (40–43). In the endocytic pathway, many ubiquitinated transmembrane proteins have been reported to be endocytosed and delivered to MVb luminal vesicles for degradation in lysosomes in both yeast and mammalian cells (1, 24, 44). The endocytic pathway also involves many cytosolic adaptor proteins that often undergo ubiquitination.

It is interesting to know what ubiquitinated proteins the GAT domain bind. The first possibility is that GGA might bind ubiquitinated transmembrane cargo proteins on TGN membranes and regulate their transport processes. In line with this possibility, the GAT-ubiquitin interaction is enhanced by ARF-GTP, which recruits GGAs onto membranes. Secondly, GGA might interact with another adaptor protein with ubiquitin modification to cooperate in trafficking processes. A third possibility is associated with our finding that, like other ubiquitin-binding proteins (30–34), GGA itself is ubiquitinated at least within the GAT domain in a manner dependent on the GAT-ubiquitin interaction. Because the GAT domain probably does not possess a ubiquitin-ligase (E3) activity, it might recruit a ubiquitin-E2 or ubiquitin-E3 intermediate. It is possible that the ubiquitin moiety appended to GGAs is recognized by another protein containing a ubiquitin-biding module.

Our attempts to explore the physiological relevance of the GAT-ubiquitin interaction have been unsuccessful so far. For example, overexpression of GGA3 mutants defective in ubiquitin binding did not affect internalization or degradation of epidermal growth factor receptor which is internalized and degraded in lysosomes in a ubiquitin-dependent manner (1, 3). The GGA3 mutants neither affected localization of cation-independent mannose 6-phosphate receptor, which is known to interact with the VHS domain of GGAs through its acidic amino acid cluster-dileucine motif (6, 8, 9). We are now searching for ubiquitinated proteins that interact with the GGA3-GAT domain through their appended ubiquitin moieties.

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