Localization of Furin to the trans-Golgi Network and Recycling from the Cell Surface Involves Ser and Tyr Residues within the Cytoplasmic Domain*

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Furin is a membrane-associated endoprotease that catalyzes cleavage of precursor proteins at Arg-X-Lys/Arg-Arg sites. Although, at steady state, furin is predominantly found in the trans-Golgi network (TGN), it also cycles between the TGN and the cell surface. Recently, the cytoplasmic tail of furin has been shown to be sufficient for its localization to the TGN. Within the cytoplasmic domain, there are Ser residues, which we now show are sites for phosphorylation by casein kinase II in vitro, and a Tyr-containing sequence, both of which have been shown to be important for other TGN proteins to localize to this compartment. In the present study, we show by site-directed mutagenesis that these residues are important for TGN localization and recycling of furin. Mutation of the Ser residues abrogated the TGN localization. By contrast, mutation of the Tyr residue did not affect the TGN localization but impaired the internalization from the plasma membrane. These observations suggest that distinct cytoplasmic determinants are responsible for retention in the TGN and retrieval from the cell surface of furin.

A novel family of mammalian processing endoproteases homologous to the yeast Kex2 protease has been shown to play a pivotal role in the production of a wide variety of biologically active peptides and proteins. These include furin, PC1/3, PC2, PC4, PACE4, and PC5/6 (for review, see Seidah et al. (1991), Steiner et al. (1992), and Halban and Irminger (1994)). Furin is a membrane-associated protease that catalyzes cleavage of a wide variety of precursor proteins at sites marked mainly by the Arg-X-Lys/Arg-Arg sequence (Bresnahan et al., 1990; Hosaka et al., 1991; Misumi et al., 1991). At steady state, furin is predominantly found in the trans-Golgi network (TGN), where it undergoes endoproteolysis (Misumi et al., 1991; Molloy et al., 1994). In addition, lines of evidence have suggested that a fraction of furin is present on the cell surface (Klimpel et al., 1992; Tsuneoka et al., 1993). Recent observations indicate that furin cycles between the cell surface and the TGN (Molloy et al., 1994). Furthermore, analyses using deletion mutants and chimeric proteins have indicated that targeting to the TGN and retrieval from the cell surface of furin requires its cytoplasmic tail (Molloy et al., 1994; Chapman and Munro, 1994; Bosshart et al., 1994).

The TGN is a compartment that appears as a tubuloreticular network extending from the trans-Golgi cisterna and plays a pivotal role in sorting of proteins within the exocytic pathway (Mellman and Simons, 1992; Ladinsky et al., 1994). Newly synthesized proteins delivered through the Golgi stacks to the TGN are packaged into different transport vesicles, which are directed to the plasma membrane, lysosomes, regulated secretory granules, and so on (Mellman and Simons, 1992; Bauerfeind and Huttner, 1993).

Signals required for localization of membrane proteins to the TGN have been extensively investigated for TGN38 and cation-dependent and cation-independent mannose 6-phosphate receptors (MPRs). In all cases, the cytoplasmic domain is responsible for the TGN localization (Kornfeld and Mellman, 1989; Kornfeld, 1992; Luzio and Banting, 1993; Stanley and Howell, 1993; Conibear and Pearse, 1994; Mauxion et al., 1995) and is capable of interacting with cytosolic transport proteins (Glickman et al., 1989; Le Borgne et al., 1993; Jones et al., 1993). Like furin, TGN38 is predominantly localized to the TGN and cycles between this compartment and the cell surface (Luzio et al., 1990; Ladinsky and Howell, 1992; Reaves et al., 1993). By mutagenesis, a Tyr-containing sequence, YQRL, in TGN38 has been shown to function as the TGN localization signal (Bos et al., 1993; Humphrey et al., 1993; Wong and Hong, 1993). MPRs are mainly localized to the TGN and endosomes and recycle between these compartments and the plasma membrane (Kornfeld and Mellman, 1989; Kornfeld, 1992). Signals within the cytoplasmic tail involved in targeting and recycling of MPRs appear to be somewhat different from those of TGN38. A Tyr-containing sequence is capable of interacting with the coat protein complex in the plasma membrane (HA-II/AP-2 clathrin adaptor) but not that in the TGN (HA-I/AP-1 clathrin adaptor) (Glickman et al., 1989) and is responsible for internalization from the cell surface rather than retention in the

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† The abbreviations used are TGN, trans-Golgi network; MPR, mannose 6-phosphate receptor; CK-II, casein kinase II; PCR, polymerase chain reaction; GST, glutathione S-transferase; MES, 4-morpholineethanesulfonic acid.
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TGN (Johnson et al., 1990; Canfield et al., 1991; Conibear and Pearse, 1994; Mauxion et al., 1995). On the other hand, a Ser residue in the MPR cytoplasmic tail, which can be phosphorylated by casein kinase II (CK-II), is involved in interaction with the HA-I/AP-1 adaptor complex and is closely associated with tyrosine phosphorylation by leucine-rich repeat kinase II (LRRK2) (Körner, 1993; Körner et al., 1994).

In the case of furin, there is a Ser-containing sequence, which fits the consensus sequence phosphorylated by CK-II (Kennelly and Krebs, 1991), and a Tyr-containing sequence, which fits the consensus sequence for phosphorylation by CK-II. Meissre and Hoflack, 1993; Körner et al., 1994). In the present study, we therefore examined the roles of phosphorylation of Tyr and Ser residues in the localization of furin to the TGN and its retrieval from the cell surface.

EXPERIMENTAL PROCEDURES

DNA Constructions—A BamHI site was introduced at the start of the cytoplasmic domain and a XhoI site after the stop codon of mouse furin cDNA (Hatsuzawa et al., 1990) by polymerase chain reaction (PCR)-based techniques. This BamHI-XhoI fragment was cloned into a glutathione S-transferase (GST) fusion vector, pGEX-4T-2 (Pharmacia Biotech Inc., Uppsala, Sweden). A HindIII-ApalI fragment covering the transmembrane and cytoplasmic domains of mouse furin, which were both made by PCR-based techniques, were cloned together between the HindIII and XhoI sites of a mammalian expression vector, pcDNA3 (Invitrogen, San Diego, CA). YA and SA mutants of the furin cytoplasmic tail were constructed by PCR of the cDNA fragment in pcDNA3 (Invitrogen, San Diego, CA) and fluorescein isothiocyanate-labeled donkey anti-mouse IgG (Chemicon, Temecula, CA). In antibody uptake experiments, cells were exposed to Leu-3a antibody (5 μg/ml) in culture for 1 h. The cells were then fixed, permeabilized, and blocked with secondary antibody. In some cases, the permeabilization step was omitted. The stained cells were observed with a laser-scanning confocal microscope (TCS4D, Leica Lasertechnik, GmbH, Heidelberg, Germany).

RESULTS

As described in the Introduction, within the furin cytoplasmic domain there is a unique Tyr residue (Tyr-758) and two Ser residues (Ser-772 and Ser-774), which lie within potential CK-II phosphorylation sites (Fig. 1). In order to examine whether these Ser residues are important for localization and recycling of furin, these residues were changed into Ala residues (Fig. 1). At first, we examined whether the Ser residues were indeed phosphorylated by CK-II. The cytoplasmic tail sequence with or without the mutation was fused with GST. The GST-furin tail fusion protein was then expressed in E. coli, purified using glutathione-Sepharose, and incubated with recombinant CK-II in the presence of [γ-32P]ATP. As shown in Fig. 2, the fusion proteins with the wild type furin tail and with the tail having the mutation of Tyr to Ala (YA mutant) were phosphorylated by CK-II. Although the identity of a minor band that migrated a little faster than the GST-fusion protein in the SDS gel is not known, it is most likely to be a degradation product of the GST-furin tail fusion protein. By contrast, the fusion protein with mutation of two Ser residues to Ala (SA mutant) was not phosphorylated. These results indicate that either or both of the two Ser residues (Ser-772 and Ser-774) can be phosphorylated by CK-II in vitro.

To examine the effects of these mutations on steady state localization of furin, the furin sequence containing the transmembrane and cytoplasmic domains with or without the mutations was fused with the extracellular domain of CD4. The expression vector was stably transfected into human hepatoma HepG2 cells. Indirect immunofluorescence microscopy with anti-CD4 monoclonal antibody revealed that strong perinuclear staining characteristic of the Golgi was observed for the CD4 fusion protein with the wild type furin sequence (Fig. 3, WT) when the cells were permeabilized after fixation (P). When the permeabilization step was omitted (NP), no staining was observed. Essentially identical results were obtained using another chimeric construct in which the cytoplasmic domain of furin was attached to the extracellular and transmembrane domains of GST fusion protein and its mutants. Substituted residues in the furin tail of the mutants are indicated. WT, wild type; Fur, furin; TM, transmembrane domain; CT, cytoplasmic tail.

Fig. 1. Schematic representation of the structures of furin tail fusion protein and its mutants. Substituted residues in the furin tail of the mutants are indicated. WT, wild type; Fur, furin; TM, transmembrane domain; CT, cytoplasmic tail.

Fig. 2. Phosphorylation by CK-II. GST (—) or GST-fusion protein with wild type (WT) furin tail or with the tail having SA or YA mutation was incubated with CK-II and [γ-32P]ATP, electrophoresed on SDS-polyacrylamide gel, and subjected to autoradiography as described under "Experimental Procedures." The position of GST-furin tail fusion protein is indicated by an arrow.

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CD4 (data not shown). These observations are in agreement with those of others (Bosshart et al., 1994; Chapman and Munro, 1994) and indicate that the cytoplasmic domain is sufficient to confer the TGN localization. In a very small fraction of cells with most intense Golgi-like staining, some punctate staining was also observed throughout the cytoplasm under permeabilized conditions, and very weak cell surface staining was observed under non-permeabilized conditions (data not shown). These observations were similar to those reported by others (Bosshart et al., 1994) and suggest a saturable mechanism for the TGN localization of furin as proposed in the case of TGN38 (Wong and Hong, 1993; Reaves and Banting, 1994). Steady state localization of the CD4-furin tail fusion protein with the YAmutation appeared not to be significantly different from that of wild type (Fig. 3, YA). By contrast, in HepG2 cells stably transfected with the construct having the SA mutation (Fig. 3, SA), perinuclear Golgi-like staining was no longer observed under permeabilized conditions. Instead, punctate structures throughout the cytoplasm were predominant. These cytoplasmic vesicles probably correspond to endosomes as reported by others (Bosshart et al., 1994; Chapman and Munro, 1994). Under non-permeabilized conditions, moderate cell surface staining was observed. In cells transfected with the construct having mutations at both Tyr and Ser residues (Fig. 3, YA/SA), more intense cell surface staining as well as punctate cytoplasmic staining was observed. We also transiently transfected the fusion constructs with or without the mutations into monkey kidney COS-7 cells and observed essentially the same staining pattern for each construct (Fig. 4).

To investigate the effects of the above mutations on recycling of the fusion protein from the cell surface, we then performed antibody uptake experiments. COS-7 cells transiently transfected with the fusion construct were incubated with anti-CD4 monoclonal antibody in culture, fixed, and processed for immunofluorescence microscopy. As shown in Fig. 5, cells transfected with the CD4-wild type furin tail construct internalized the antibody and localized it predominantly to a perinuclear Golgi region. This result was in good agreement with that reported by others (Molloy et al., 1994; Chapman and Munro, 1994). In cells expressing the fusion protein with the YA mutation, the antibody uptake was inefficient. Non-permeabilized cells showed intense cell surface staining. Furthermore, many endosome-like vesicles were stained, although a perinuclear region was also significantly stained. These results suggest that the YA mutation causes retardation in endocytosis of the fusion protein from the plasma membrane. By contrast, in cells expressing the fusion protein with the SA mutation, cell surface localization of Furin to TGN

![Fig. 3. Steady state localization of CD4-furin tail chimeras in stably transfected HepG2 cells.](http://www.jbc.org/)

![Fig. 4. Steady state localization of CD4-furin tail chimeras in transiently transfected COS-7 cells.](http://www.jbc.org/)
staining was barely detectable. However, no Golgi-like staining was observed, and endosome-like staining was prominent. These observations suggest that although the SA mutant is indeed endocytosed from the plasma membrane to endosomes, it is unable to move from endosomes to the TGN. The staining pattern observed in cells expressing the chimera with both YA and SA mutations appeared to be most different from that in wild type-expressing cells. Intense cell surface staining and no Golgi-like staining were observed.

DISCUSSION

Furin was first found to be predominantly localized to the TGN, but more recent studies have shown that it also cycles between the TGN and the cell surface (Molloy et al., 1994) and that its cytoplasmic tail is necessary and sufficient to confer the correct localization and recycling (Molloy et al., 1994; Chapman and Munro, 1994; Bosshart et al., 1994). We noted that the cytoplasmic domain of furin contains (i) a unique Tyr residue within a sequence reminiscent of previously described Tyr-containing TGN localization motifs and (ii) two Ser residues that lie within consensus CK-II sites. In the present study, we examined if these residues were important for TGN localization and recycling by expressing chimeras of the CD4 ectodomain and the transmembrane and cytoplasmic domains of furin.

When the Tyr was mutated to Ala, retention of the fusion protein in the TGN appeared not to be impaired. However, its retrieval from the plasma membrane to the TGN was significantly retarded (Fig. 5). A similar phenomenon has been reported in the case of MPRs, which are also present in the TGN and cycle between this compartment and the cell surface (Conibear and Pearse, 1994; Mauxion et al., 1995). Previous studies have established that there are internalization signals containing unique Tyr residues within the cytoplasmic domains of constitutively recycling receptors (for review, see Trowbridge (1991), Luzio and Banting (1993), and Sandoval and Bakke (1994)). When receptors such as low density lipoprotein and transferrin receptors bind their ligands at the plasma membrane, they undergo rapid internalization and are delivered to endosomes. Here they release their bound ligands and recycle back to the cell surface. Thus, the Tyr-containing sequence is a signal for delivery of these receptors from the cell surface to endosomes. The data we presented here show that this is also true for furin.

We confirmed that the Ser residues can be phosphorylated by CK-II in vitro. The data presented here indicate that the Ser residues are important for the TGN localization of furin, although it is unknown whether these residues are phosphorylated in vivo. When the Ser residues were mutated to Ala, the CD4-furin chimera was no longer retained in the TGN; instead it was predominantly found in endosome-like structures and at the plasma membrane. An antibody uptake experiment showed that the SA mutant chimera was indeed internalized from the cell surface but did not reach to the TGN. The delivery of the chimera from the cell surface appeared to be blocked in an endosomal compartment. That furin passes through endosomes on its way from the cell surface to the TGN has been demonstrated by the recent data of Chapman and Munro (1994). They
have shown that internalization of a furin chimera is blocked at endosomes when cells expressing the chimera are treated with chloroquine, which neutralizes acidic organelles. In this concern, the data of Bosshart et al. (1994) are also noteworthy. They have provided evidence that a fraction of furin molecules is delivered to a lysosomal compartment for degradation, although it is unclear whether routing of furin to lysosomes occurs directly from an internal site or involves a round of transport through the cell surface. Taken together, we postulate either or both of the following possibilities for the role of the Ser residues. One is that the Ser residues are essential for retention of furin molecules in the TGN. This is supported by the data that the SA mutant is localized to endosomes and the plasma membrane at steady state. The other possibility is that the Ser residues are involved in retrieval from endosomes to the TGN of furin molecules, which have gone out of the TGN to endosomes or are internalized from the plasma membrane to endosomes.

The observations for the YA/S4 mutant support the above mentioned roles of the Tyr and Ser residues. Both retention in the TGN and internalization from the cell surface of the YA/S4 chimera were severely impaired. Fig. 6 illustrates the models for trafficking of furin and its mutants on the basis of the observations presented here and the data of others (Chapman and Munro, 1994; Bosshart et al., 1994). Basically, the majority of furin molecules are retained in the TGN. A saturable mechanism may underlie the retention as proposed in the case of TGN38 (Hong and Wong, 1993; Reaves and Banting, 1994). A fraction of the molecules released from the TGN retention may be delivered to the plasma membrane and cycle back to the TGN via endosomes and/or may be directly delivered to endosomes. Then, the molecules in endosomes may return to the TGN. Our data indicate that, to confer correct TGN localization, the cytoplasmic tail of furin contains at least two signals: the Tyr residue that is involved in internalization from the cell surface to endosomes and the Ser residues that can be phosphorylated by CK-II in vitro and are involved in retention in and retrieval from endosomes to the TGN. However, whether phosphorylation of these residues regulates localization of furin in vivo is yet to be determined.

In MPRs, HA-I/AP-2 plasma membrane adaptor has been shown to interact with a Tyr-containing sequence (Glickman et al., 1989), and HA-I/AP-1 Golgi adaptor has been suggested to recognize another region of the cytoplasmic tail, probably the Ser residues of the consensus CK-II sites (Glickman et al., 1989; Le Borgne et al., 1993). Furthermore, Méresse et al. (1990) have shown that the Ser residues are phosphorylated by a CK-II-like activity associated with the HA-I/AP-1 adaptor. These data are compatible with the notion that the Tyr and Ser residues are involved in retrieval from the plasma membrane and retention in the TGN, respectively, of MPRs. Taken together with the data presented here, we think that similar mechanisms underlie localization to the TGN and recycling of furin. By contrast, in the case of another TGN-resident protein, TGN38, the Tyr-containing motif appears to be responsible for both retention in the TGN and retrieval from the cell surface (Bos et al., 1993). However, there is a report showing that a Ser residue, which is positioned two residues upstream of the Tyr, is also important for the TGN retention (Hong and Wong, 1993). Furthermore, Ponnambalam et al. (1994) have shown that not only the cytoplasmic tail but also the transmembrane domain of TGN38 is implicated in its correct localization. Thus, the localization mechanisms of TGN38 may be somewhat different from those of furin and MPRs. Recently, a protein complex including an unidentified protein of 62 kDa and Rab6 has been reported to be capable of binding the TGN38 cytoplasmic tail (Jones et al., 1993). However, it has not been examined if the cytoplasmic tail can interact with the clathrin adaptor complexes. Further analyses on interaction between the cytoplasmic tail of the TGN38 protein and cytosolic factors will be required to understand the mechanisms underlying retention in the TGN and recycling of these proteins.

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