HHS Public Access

Author manuscript

Traffic. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Traffic. 2019 February ; 20(2): 110–120. doi:10.1111/tra.12624.

Mechanisms of the Anterograde Trafficking of GPCRs: Regulation of AT1R Transport by Interacting Proteins and Motifs

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Abstract

Anterograde cell surface transport of nascent G protein-coupled receptors (GPCRs) *en route* from the endoplasmic reticulum (ER) through the Golgi apparatus represents a crucial checkpoint to control the amount of the receptors at the functional destination and the strength of receptor activation-elicited cellular responses. However, as compared with extensively studied internalization and recycling processes, the molecular mechanisms of cell surface trafficking of GPCRs are relatively less defined. Here, we will review the current advances in understanding the ER-Golgi-cell surface transport of GPCRs and use angiotensin II type 1 receptor as a representative GPCR to discuss emerging roles of receptor-interacting proteins and specific motifs embedded within the receptors in controlling the forward traffic of GPCRs along the biosynthetic pathway.

Keywords

angiotensin II type 1 receptor; anterograde trafficking; biosynthesis; cell surface expression; C-terminus; endoplasmic reticulum; export; Golgi; G protein-coupled receptor; interacting protein; maturation; motif; signaling

Anterograde transport of GPCRs

G protein-coupled receptors (GPCRs) constitute the largest and most structurally diverse superfamily of membrane signaling proteins and modulate a wide variety of physiological and pathological functions. The functions of GPCRs are mediated through coupling to heterotrimeric G proteins, arrestins and other signaling molecules which in turn activate downstream effectors, such as protein kinases, adenylyl cyclases, phospholipases and ion channels. One important factor that crucially regulates the precise function of the receptors is their intracellular trafficking, including anterograde cell surface transport, endocytosis, recycling, and lysosomal degradation, which control the number of the receptors at the cell surface, the functional destination for most GPCRs, which in turn dictates the magnitude of

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Conflict of interest The authors have no conflict of interest to declare.

receptor activation-elicited cellular responses at a given time. However, as compared with well-characterized internalization and recycling, the molecular mechanisms underlying the cell surface transport of nascent GPCRs are relatively less well understood.

Similar to many other plasma membrane proteins, the life of GPCRs begins at the endoplasmic reticulum (ER), where they are synthesized, folded and assembled. Correctly folded and properly assembled receptors are able to pass the ER quality-control system, move forward from the ER to the cell surface, en route pass through the ER-Golgi intermediate complex (ERGIC), Golgi cisternae, and trans-Golgi network (TGN), during which the receptors may undergo post-translational modifications to attain a fully mature status. Emerging evidence from the studies in recent years suggest that the cell surface transport of GPCRs is regulatable, mediated through multiple pathways, and in a cell type and receptor specific manner. The most significant progress towards the understanding of anterograde transport of GPCRs is the identification of a number of regulatory proteins (Table 1), which may function as chaperones, escort proteins, gatekeepers, transport machinery, sorting molecules or signaling proteins to regulate receptor correct folding, maturation, assembly, recruitment onto the transport vesicles, retention in and export from the ER and Golgi compartments, sorting from other plasma membrane proteins or other GPCRs, transportation along the microtubule network, and delivery to the plasma membrane. As demonstrated in different protein-protein interaction assays, many of these regulatory proteins are able to directly interact with the receptors they regulate and thus, by virtue of their ability to interact with selective GPCRs, some of these regulatory proteins may only regulate the cell surface transport of a specific GPCR, while others may influence the transport of a group of GPCRs. It is also of interest to note that the final impact of these regulatory proteins on the cell surface expression of the receptors could be beneficial or deleterious.

Another important progress achieved over the past years is that a number of specific motifs embedded within the receptors have been revealed to be required for the cell surface transport of GPCRs, such as the $E(x)_3LL$ motif in vasopressin receptor 2 (V2R)[88], the $F/Y(x)_3F(x)_3F$ motif in dopamine D1 receptor (D1R)[15] and neuropeptide Y receptor type 2[89], the $FN(x)_2LL(x)_3L$ motif in vasopressin V1b/V3 receptor[90], the $F(x)_6LL$ motif in α_{2B}-adrenergic receptor (AR), angiotensin II (Ang II) type 1 receptor (AT1R), α_{1B}-AR, β_2-AR and M1-muscarinic receptor (MR)[91–93], the YS motif in α_{2A}-AR and α_{2B}-AR[94] , the VxPx motif in rhodopsin[4,5,82], the RRR and $R(x)_3R(x)_4R$ motifs in α_{2B}-AR[23,83,95], di-acidic and di-basic motifs in AT1R, AT2R and GPR15[84,96,97], and serine-rich motifs in melanocortin 5 receptor[98]. These motifs may regulate receptor correct folding, function as independent export signals to dictate receptor exit from the ER or the Golgi or as retention motifs to prevent receptor export from intracellular compartments, or provide docking sites for regulatory proteins.

In addition, the constitutive dimerization (including homo- and hetero-dimerization) in the ER and post-translational modifications of GPCRs also regulate their cell surface transport. For example, γ-aminobutyric acid B1 receptor (GABABR1) has an ER retention motif at its C-terminus and thus, when expressed alone it is retained in the ER, unable to transport to the cell surface. When co-expressed with GABABR2, it forms hetero-dimers with GABABR2

which masks the ER retention signal, leading to the ER export and cell surface transport[99,100]. Glycosylation at Asn residues and palmitoylation at Cys residues are the most common post-translational modifications of GPCRs which have been well demonstrated to play an important role in the maturation and cell surface transport of some GPCRs[101–105]. AT1R possesses three Asn-linked glycosylation sites at positions 4, 176 and 188 and glycosylation is absolutely required for its cell surface expression[101,102]. AT1R also has a Cys residue at position 355 in the distal C-terminal region which is in marked contrast to many other GPCRs containing Cys residues next to helix 8 which anchor the helix 8 to the plasma membrane. However, the effect of Cys355 on the cell surface transport of AT1R remains to be determined.

Next, we will use AT1R as a representative GPCR to discuss in more detail the function of specific motifs and regulatory proteins that may interact with these motifs in regulating AT1R transport to the cell surface. We will also discuss the relevance of transport mechanisms of AT1R to the anterograde trafficking of other GPCR members.

The role of the C-terminus in the trafficking and signaling of AT1R

Ang II is the major biologically active hormone produced by the renin-angiotensin system (RAS) and plays an important role in the maintenance of blood pressure and fluid homeostasis. The dysregulation of Ang II and the RAS directly contributes to a number of human diseases, such as hypertension, cardiac hypertrophy, congestive heart failure, stroke and diabetic nephropathy. The function of Ang II is mainly mediated through activating its cell surface receptors including AT1R and AT2R, both belong to the GPCR superfamily. There is only one AT1R subtype in human, whereas two AT1R subtypes, AT1aR and AT1bR which share 95% amino acid sequence identity, exist in rat and mouse[106–108]. As demonstrated in many studies, it is AT1R that mediates the most physiological actions of Ang II. Although AT2R has been suggested to counterbalance the actions of AT1R and genetic mutations of AT2R were associated with X-linked mental retardation[109], the exact physiological functions of AT2R remain elusive.

AT1R couples to the Gq family G proteins and regulates a variety of signal transduction pathways, involving the activation of voltage-gated Ca^{2+} channels, phospholipases (PLC, PLD and PLA2), and mitogen-activated protein kinases (MAPK). In addition to G protein-dependent signaling pathways, AT1R is also able to activate several G protein-independent signaling pathways, such as those mediated via β-arrestins, which were initially identified to mediate GPCR internalization from the plasma membrane to the endosomal compartment and function as negative regulators of GPCR- and G protein-mediated signaling. More interestingly, recent studies have revealed that some AT1R ligands can preferentially activate one pathway and are therefore referred to as biased agonists. For example, the peptides TRV120023, TRV120027 and TRV120067 are β-arrestin-biased AT1R agonists which have been demonstrated to have beneficial cardiovascular effects in animal studies[110,111].

AT1R has three short intracellular loops and a relatively large C-terminus. The C-terminus of AT1R possesses an amphipathic 8^{th} α-helix in the membrane-proximal region (Fig. 1) and is the most important intracellular domain in the regulation of receptor functions,

including G protein coupling, signaling, trafficking, phosphorylation and interaction with cytosolic proteins[112–120] (Table 2). Based on the newly published high resolution crystal structures of truncated AT1R lacking the C-terminal forty residues after helix 8 in complex with an antagonist ZD7155[121], the helix 8 of AT1R runs away from the membrane which is apparently different from other GPCRs in which the helix 8 is parallel to the membrane bilayer.

The crucial role of the C-termini in the ER export and cell surface transport has been known for a number of GPCRs, including AT1R[15,90,91,135,136]. The AT1R mutants lacking the C-terminus were arrested in the ER as indicated by extensive co-localization with the ER markers, unable to transport to the cell surface. Further mutagenesis of the C-terminus revealed several motifs essential for AT1R exit from the ER and subsequent transport to the Golgi and the cell surface[91,137] (Fig. 1). Interestingly, these motifs may mediate AT1R interaction with specific regulatory proteins involved in the cell surface transport of the receptor.

The C-terminal hydrophobic motifs and their interacting proteins in the cell surface transport of AT1R

The $F(x)_6LL$ motif and GABARAP

The $F(x)_6LL$ motif (where x can be any residue and L is leucine or isoleucine) is highly conserved in the membrane-proximal C-termini of the family A GPCRs[91]. For AT1R, F309 and L316L317 in the C-terminus were identified to form an essential motif for the ER export and cell surface transport. Mutation of F309 and L316L317 individually or in combination abolished AT1R cell surface expression with intensive ER accumulation. Consistent with the loss of the ability to move to the cell surface, the mutated receptors were unable to initiate downstream signaling measured as the activation of the MAPK ERK1/2 in response to Ang II stimulation[91].

In addition to AT1R, mutation of the $F(x)_6LL$ motif also markedly attenuated the ER export and cell surface transport of α_{2B}-AR, β_2-AR, α_{1B}-AR and M1-MR[91,92,138], implicating a general role of this motif in the anterograde traffic of family A GPCRs. Although the exact molecular mechanisms underlying the function of the $F(x)_6LL$ motif remain largely unknown, several studies suggest that it may modulate multiple events in the anterograde trafficking of GPCRs. Because the membrane-proximal C-termini of these GPCRs form structurally an α-helix, it has been postulated that these hydrophobic motifs are involved in the correct folding of GPCRs. It is also possible that the F and LL residues may regulate different aspects of receptor trafficking in which F is likely involved in folding of the receptor, possibly through interaction with other hydrophobic residues in neighboring domains[92], whereas the LL sequence may function as an independent ER export signal, autonomously directing receptor export from the ER. Consistent with this possibility, the di-hydrophobic motifs, such as FF, have been demonstrated to function as ER export motifs[139–143]. Recent studies have also demonstrated that this motif may mediate receptor interaction with Rab1, Rab8 and a γ-aminobutyric acid receptor-associated protein

(GABARAP)[25,57,144], all of which have been shown to regulate the cell surface transport of GPCRs.

GABARAP was originally identified through its binding to one subunit of the pentameric ionotropic γ-aminobutyric acid type A receptor (GABAAR) to regulate the plasma membrane transport via the microtubule tracks and to affect both the clustering and kinetic properties of the receptor. GABARAP was then identified as a binding partner for the C-terminus of AT1R in a yeast two-hybrid mouse brain library screening[25]. The interaction between GABARAP and AT1R was further confirmed by several protein-protein assays (GST fusion protein pull-down, co-immunoprecipitation and bioluminescence resonance energy transfer assays). Importantly, enhanced expression of GABARAP promoted AT1R cell surface expression whereas depletion of GABARAP by siRNA produced an opposing effect, indicating that GABARAP is involved in regulation of AT1R transport to the cell surface. The follow-up studies demonstrated that mutation of the $F(x)_6LL$ motif abolished the interaction of AT1R with GABARAP[127], suggesting that GABARAP may bind to the $F(x)_6LL$ motif in the C-terminus of AT1R. However, it remains unknown if GABARAP is able to interact with other GPCRs which carry the $F(x)_6LL$ motif. Nevertheless, these data provide insights into the function of the $F(x)_6LL$ motif and the interacting protein GABARAP in regulating AT1R transport.

The caveolin-binding like motif YxFxxxxFxxY and the interacting proteins caveolin and DRiP78

Several studies suggest that the aromatic residues in the caveolin-binding-like motif YxFxxxxFxxY in the C-terminus are important for the optimal expression of AT1R at the plasma membrane[9,10,137]. Mutation of the YxFxxxxFxxY motif inhibited AT1R expression at the plasma membrane and the receptors were largely expressed in the perinuclear region. Caveolin-3 was shown to directly interact with AT1R through the caveolin scaffolding domain[10]. Most convincing data indicating that caveolin participated in the maturation of AT1R were generated from caveolin-1 knockout mice in which AT1R transport to the cell surface was significantly attenuated[10]. It was proposed that the interaction between AT1R and caveolin occurs likely during the export process between the ER and the Golgi and caveolin acts as a molecular chaperone to enhance AT1R transport to the cell surface.

Dopamine receptor-interacting protein 78 (DRiP78) is an ER membrane-associated chaperone protein belonging to the DnaJ/Hsp40 class. It was initially found as a dopamine D1 receptor (D1R)-associated protein by binding to the C-terminal FxxxFxxxF motif. Interestingly, either overexpression of DRiP78 or incubation with the C-terminal peptide to disrupt the interaction between DRiP78 and D1R induced the retention of D1R in the ER and slowed down receptor maturation, suggesting a strictly moderate level of endogenous DRiP78 available for association is important for efficient export of D1R from the ER[15]. In addition to D1R, the export trafficking of other GPCRs, including AT1R, was also regulated by DRiP78[9]. In contrast to the inhibitory effect on D1 receptor, the expression of DRiP78 enhanced the plasma membrane expression of AT1R. However, the cell surface expression of the AT1R mutant in which the motif YxFxxxxFxxY was mutated was not affected by DRiP78, suggesting a functional interaction between DRiP78 and AT1R[9].

The C-terminal charged motifs and their interacting proteins in the cell surface transport of AT1R

The di-basic motif KK and tubulin

There are four positively charged residues at positions 307, 308, 310 and 311 in the C-terminal membrane-proximal region of AT1R (Fig. 1). This positive cluster was shown to be required for the high affinity binding of the receptor to the negatively charged lipids of the plasma membrane[145–147], to contain a nuclear localization signal which mediates AT1R translocation into the nucleus[148,149], and to influence the total synthesis of the receptor[150].

In GST fusion protein pulldown assays to search for interacting proteins using the C-terminus of α_{2B}-AR as bait, tubulin was identified as an interacting protein of α_{2B}-AR[83]. Further mutagenesis analysis of the C-terminus identified R437, R441 and R446 in the membrane-proximal region responsible for tubulin interaction. Subsequent studies revealed that tubulin also directly and strongly bound to AT1R (and α_{2A}-AR, but not β_2-AR)[85] and the interaction domains were mapped to two consecutive Lys residues at positions 310 and 311 in the C-terminal membrane-proximal region of AT1R and the acidic C-terminus of tubulin[84], suggesting that the interaction of AT1R and α_{2B}-AR with tubulin is ionic in nature. Importantly, mutation of these Lys residues significantly inhibited receptor transport to the cell surface and the receptor mutants were extensively arrested in the ER[84]. These data suggest that AT1R (as well as other GPCRs such as α_2-ARs) may directly contact with the microtubule network to coordinate its own ER-to-cell surface traffic.

The di-acidic ExE motif and ER export

Protein export from the ER is a selective process that is exclusively mediated through COPII-coated transport vesicles. In order to be efficiently exported in COPII vesicles, cargo proteins, particularly transmembrane proteins, may specifically interact with the components of COPII vesicles via ER export motifs which are short, linear sequences presented in the C-termini of cargo proteins. Of various ER export motifs identified, the di-acidic motifs have been found in the cytoplasmic C-termini of several membrane proteins, such as vesicular stomatitis virus glycoprotein (VSVG), cystic fibrosis transmembrane conductance regulator, and potassium channels to direct their export from the ER[151–155].

The di-acidic ExD motif in the membrane-distal, nonstructural C-terminal portion of the rat AT2R and the ExE motif in the human AT2R were shown to play an obligatory role in receptor forward trafficking to the cell surface[96]. These motifs likely control receptor exit from the ER, as their mutants were accumulated in the ER. More interestingly, the export ability of each acidic residue in the di-acidic motifs cannot be fully substituted by other acidic residue, suggesting that distinct di-acidic motifs dictate optimal export trafficking of different AT2R. Moreover, the function of the di-acidic motifs in AT2R export is likely mediated through facilitating the recruitment of the cargo receptors onto the ER-derived COPII transport vesicles[96].

Similar to AT2R, the cell surface expression of AT1R was attenuated by mutation of the motif ExE in the very end of the C-terminus (Fig. 1), indicating an important role of the di-

acidic ExE motif in AT1R forward trafficking[96]. However, in contrast to AT1R and AT2R, the cell surface expression of β_2-AR and α_{1B}-AR was not altered by mutating the di-acidic motifs in their C-termini[96]. Therefore, the di-acidic motifs located in the membrane-distal C-termini may represent the first linear motifs which selectively recruit the Ang II receptors onto the COPII vesicles to control their export from the ER. However, it remains to be determined if these di-acidic motifs are able to mediate receptor interaction with any components of COPII vesicles.

The C-terminal helix 8 and small GTPases in the cell surface transport and sorting of AT1R

The helix 8 and Rab43

Consisting of more than 70 members, Rab GTPases form the largest subfamily of Ras-related small GTPases and are master regulators to coordinate almost every step of vesicle-mediated membrane transport, including cargo selection, vesicle formation, sorting, motility, tethering and fusion with the appropriate membranes. Several Rabs, including Rab4, Rab5, Rab7 and Rab11 have been shown to interact with the same domain in the C-terminus of AT1R to regulate receptor phosphorylation, internalization, recycling and lysosomal transport (Table 2).

As an initial approach to investigate the role of Rab GTPases in the anterograde transport of GPCRs, we determined the role of Rab1 in the cell surface transport of several GPCRs. Rab1 is the best characterized and well understood Rab GTPase, which localizes in the ER and the Golgi and regulates anterograde transport specifically from the ER to the Golgi and between the Golgi compartments. We found that transient expression of dominant-negative Rab1 mutants and siRNA-mediated depletion of Rab1 significantly reduced the cell surface expression of AT1R in HEK293 cells[50], cardiac myocytes[53] and vascular smooth muscle cells[54]. Consistently, inhibiting Rab1 function attenuates Ang II-mediated signaling, cardiomyocyte hypertrophic responses and smooth muscle cell phenotypic regulation[50,53–55]. In contrast to Rab1, Rab6 was shown to regulate the retrograde trafficking from the late to early Golgi cisternae and from the Golgi to the ER. Despite Rab1 and Rab6 control opposite transport in the early secretory pathway, the expression of Rab6 mutants also reduced the cell surface expression of AT1R[58].

Rab43 was recently identified to control the cell surface transport of several GPCRs, including AT1R, but had no effect on the transport of non-GPCR transmembrane proteins epidermal growth factor receptor and VSVG[66]. Similar to Rab1, Rab43 is localized to the ER and Golgi, but its function is poorly studied. As expression of dominant negative Rab43 mutants and siRNA-mediated depletion of Rab43 significantly arrested AT1R in the ER and reduced the acquisition of complex N-linked glycosylation of AT1R, Rab43 specifically controls AT1R transport from the ER to the Golgi. More interestingly, Rab43 was shown to directly interact with AT1R and the interaction domain was mapped to the C-terminal 8th α-helix region. These data suggest that AT1R may physically associate with components of the transport machinery to control its transport to the cell surface en route from the ER.

In addition to mediating GPCR forward transport, Rab43 may also play an important role in separating GPCRs from other plasma membrane proteins during maturation processing. Although GPCRs share a common structural topology and several proteins have been identified to control the sorting of GPCRs at the endosomal and lysosomal compartments after internalization[156–165], how they are sorted from other plasma proteins at the ER level after their synthesis and then transported via specific routes are poorly understood. The Rab43-binding domain identified in the AT1R C-terminus was able to effectively convert the Rab43-independent transport of VSVG into Rab43-dependnet transport, specifically from the ER to the Golgi. These data provide strong evidence indicating that Rab43 controls not only ER-to-Golgi transport but also the ER sorting of AT1R and possibly other GPCR members by virtue of its ability to directly interact with the receptors.

ARF1/Sar1 family GTPases

Sar1 and six ARF GTPases belong to the same subfamily of Ras-like GTPases and are well characterized to play crucial roles in the formation and budding of different transport vesicles. In particular, Sar1 GTPase recruits the Sec23/24 and Sec13/31 complexes onto the ER membrane, leading to the formation of the COPII-coated vesicles. ARF1 is able to recruit different sets of coat proteins to form distinct transport vesicles that control protein transport at different intracellular organelles. In the early secretory pathway, ARF1 recruits a complex of cytosolic proteins, collectively known as coatomers, leading to the formation of COPI vesicles which mediate protein transport from the Golgi to the ER or from the ER-Golgi intermediate complex (ERGIC) to the Golgi and intra-Golgi traffic. In the post-Golgi transport, ARF1 interacts with adaptor proteins and Golgi-localized, γ-adaptin ear domain homology, ADP ribosylation factor-binding proteins (GGAs), both of which recruit clathrin onto the TGN, forming the clathrin-coated vesicles that mediate post-Golgi transport between the TGN, the plasma membrane and the endosomal compartment.

The role of Sar1 GTPase in the cell surface transport of GPCRs has been determined by transient expression of a GTP-restricted Sar1 mutant (Sar1H79G)[76,77], which functions as a dominant negative mutant to block the release of the COPII vesicles from the ER membrane. Expression of Sar1H79G significantly attenuated the cell surface expression of AT1R[76] and the receptors were extensively co-localized with GM130, a cis-Golgi marker which has been demonstrated to translocate from the cis-Golgi to ER exit sites in the presence of Sar1H79G. These data suggest that AT1R is able to export from the ER to ER exit sites in the cells expressing Sar1H79G. It is interesting to note that expression of Sar1H79G blocked the cell surface transport of several other GPCRs, but differentially regulates ER export of different GPCRs[76,77].

The role of ARF1 in the cell surface transport of GPCRs including AT1R has also been studied[2]. Although the expression of GDP- and GTP-bound ARF1 mutants markedly reduced the cell surface transport of AT1R, they arrested the receptors in distinct intracellular compartments. Whereas expression of the GDP-bound mutant ARF1T31N arrested AT1R in the ER, the GTP-bound mutant ARF1Q71L induced an accumulation of the receptors in the post-ER compartments[2]. These data indicate that expression of different ARF1 mutants blocks the export of the cargo receptors from different subcellular

compartments, consistent with multiple functions of ARF1 in the formation of different transport vesicles from distinct compartments. Altogether, the Ras-like small GTPases Rab1, Rab6, Rab43, Sar1 and ARF1 control the anterograde trafficking of AT1R, each may regulate the transport at distinct steps (e.g. recruitment onto COPII vesicles, ER export, ER-Golgi transport or Golgi-plasma membrane transport) (Fig. 2).

Other AT1R-interacting proteins involved in the cell surface transport

The C-terminal interaction with CD74

CD74 is a type II transmembrane protein and acts as a chaperone for the trafficking of the major histocompatibility complex class II molecules. By using the yeast two-hybrid approach to screen a human kidney cDNA library, Szaszák et al. identified CD74 as an interacting protein for the AT1R C-terminus[12]. The interaction between AT1R and CD74 was verified by co-immunoprecipitation and co-localization assays. The CD74-binding site was mapped to the C-terminal membrane proximal region of AT1R. Interestingly, CD74 overexpression markedly reduced the cell surface expression of ATR and induced receptor accumulation in the ER and targeting to the proteasomal degradation pathway. These data suggest that, in contrast to other interacting proteins which promote the cell surface expression of AT1R, CD74 is likely a negative regulator of AT1R trafficking along the biosynthesis pathway.

AT1R interaction with chaperon proteins

In addition to DRiP78 as discussed above, several other chaperone proteins, including calnexin, Hsp70 and calreticulin, have also been shown to interact with AT1R and their interactions with the no-glycosylated AT1R mutant were stronger than with wild type AT1R[166]. Similarly, several ER-export deficient, misfolded GPCR mutants exhibited strong interactions with chaperone proteins[167–169]. These data suggest that ER chaperones may have a duel function in regulating GPCRs, not only promoting proper folding of the immature receptors but also preventing the export of terminally misfolded receptors from the ER to the Golgi.

AT1R interaction with RACK1

Receptor for activated C kinase 1 (RACK1) was identified to interact with the C-terminus and the first intracellular loop of the β isoform of thromboxane A2 receptor (TBβ) in yeast two-hybrid and GST fusion protein pulldown assays[67]. The fact that overexpression of RACK1 and its depletion by siRNA produced opposing effects on the cell surface expression of TBβ indicates an important role played by RACK1 in the cell surface traffic of TBβ. In addition to TBβ, the cell surface expression of CXCR4 and AT1R was also attenuated by siRNA-mediated knockdown of RACK1 and AT1R physically associated with AT1R as measured in coimmunoprecipitation assays[67]. As siRNA-mediated knockdown of RACK1 arrested the receptors in the ER, RACK1 is most likely involved in the ER-to-Golgi transport.

Concluding remarks

Over the past decade great progress has been made in elucidating molecular mechanisms underlying the anterograde transport of newly synthesized GPCRs en route from the ER through the Golgi body. It is increasingly apparent that, similar to the endocytic pathways, the cell surface transport of GPCRs is a complicate, highly coordinated process. In particular, multiple regulatory proteins have been identified to control receptor trafficking via direct interaction with the receptors at specific domains and these protein-protein interactions may lead to the formation of specialized transport machineries that drive the forward traffic of the receptors. However, the relationship between these interacting proteins and how they cooperate to ensure normal receptor export from the ER to the cell surface of GPCRs in general or AT1R in particular need further investigation. It is possible that multiple routes exist to mediate receptor cell surface transport, either from the ER to the Golgi or from the Golgi to the plasma membrane, and each route requires a group of distinct regulatory proteins. Since the abnormal plasma membrane expression, mistrafficking, and dysfunction of many GPCRs, including AT1R, are clearly implicated in the pathogenesis of a variety of human diseases, including neurological disorders, cardiovascular diseases, and cancer[107], to further explore the regulatory mechanism of anterograde transport of GPCRs may provide an important foundation for developing new therapeutic means in treating human diseases involving abnormal trafficking and signaling of the receptors.

Acknowledgements

This work was supported by National Institutes of Health Grant R01GM118915 (to G. Wu) and National Natural Science Foundation of China Grant 31771300 (to M. Zhang). We apologize to numerous colleagues whose work could not be cited in this article due to space limitation.

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Synopsis:

As compared with internalization and recycling, anterograde cell surface transport of nascent GPCRs *en route* from the endoplasmic reticulum through the Golgi apparatus remains poorly understood. Here, we will review the current understanding of the cell surface trafficking of the GPCR superfamily and use AT1R as an example to discuss emerging roles of receptor-interacting proteins and specific motifs.

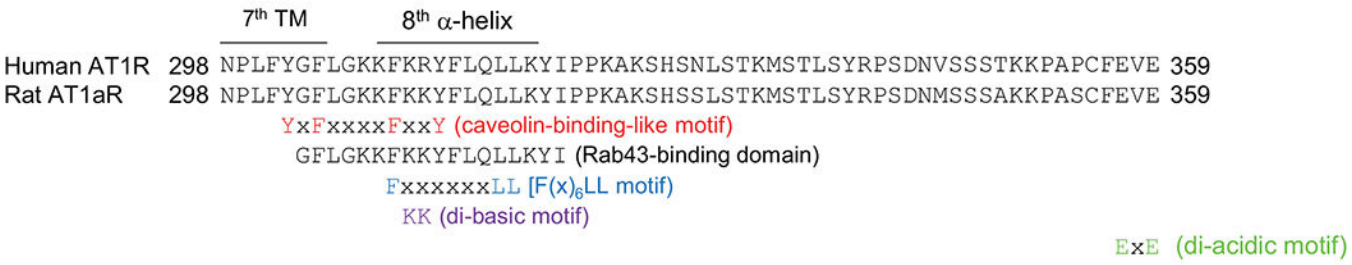

Fig. 1. Specific motifs identified in the C-terminus of AT1R involved in anterograde cell surface trafficking.

TM, transmembrane domain.

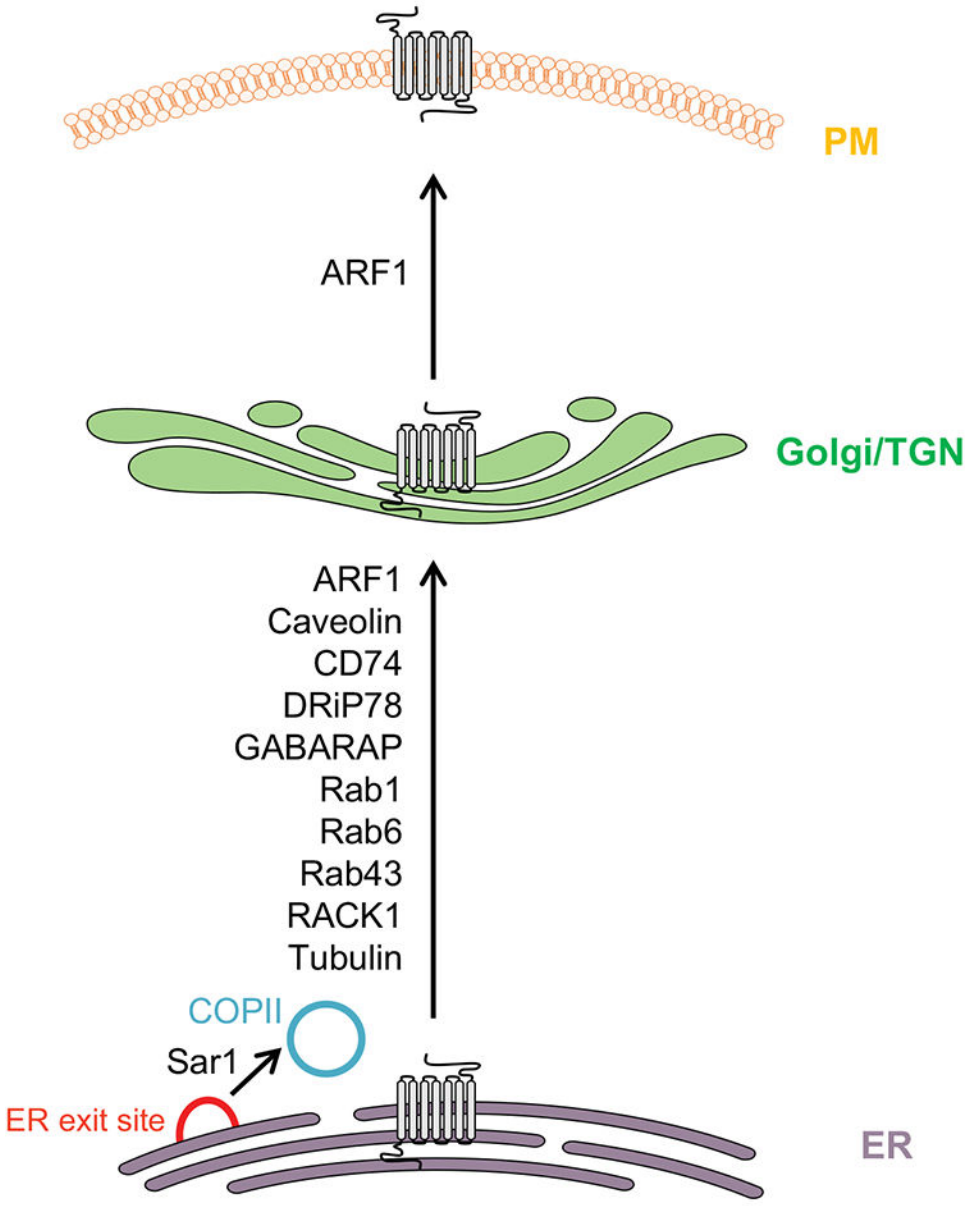

Fig. 2. Regulatory proteins involved in the ER-Golgi-plasma membrane (PM) transport of AT1R.
See text for detail.

Table 1.

Some of the regulatory proteins involved in the anterograde cell surface transport of GPCRs

Regulatory proteins	GPCRs	References
14-3-3	CaSR	1
ARF1	α_{2B}-AR, β_2-AR, AT1R, CXCR4, M3-MR, PAR-2	2,3
ARF3	α_{2B}-AR	2
ARF4	Rhodopsin	4,5
ARF5	α_{2B}-AR	2
ARF6	α_{2B}-AR, V1aR, V2R, M2-MR	2,6
ATIP1/ATBP50	AT2R	7,8
Caveolin	AT1R	9,10
CD4	CCR5	11
CD74	AT1R	12
CLIC4	H3R	13
CNIH4	β_2-AR, CCR5	14
DRiP78	D1R, M2-MR, AT1R, CCR5	9,15,16
Filamin-2	α_{2C}-AR	17
Filamin A	D2R	18
gC1q-R	α_{1B}-AR	19
GEC1	KOR, EP3R	20,21
GGAs	α_{2B}-AR	22,23
Golgin-160	β_1-AR	24
GABARAP	AT1R	25
Homer 1	mGluR1a, mGluR5	26,27
HSJ1b	Rhodopsin	28
Kif5B	5-HT_{1A}R	29
M10	VN2R	30
MRAP/MRAP2	MCR	31
Neurofilament-M	D1R	32
NinaA	Rhodopsin	33
ODR-4	ODR-10, U131, STR112, STR113,	34–36
P11	5-HT_{1B}R	37
P23/P24A	PAR-2, MOR, $P2Y_4$R	38
PAPLA1	Rhodopsin	39
PI3K C2A	DOR	40
Pontin	α_{2C}-AR	41
PRAF2	$GABA_B$R	42
Protachykinin	DOR	43
Protein 4.1G	A1AR, PTHR, mGluR1a	44–46
Protein 4.1N	D2R, D3R	47

Regulatory proteins	GPCRs	References
PTEN	DOR	48
Rab1	α_{1A}-AR, α_{1B}-AR, β_1-AR, β_2-AR, AT1R, AT2R, hCaR	49–57
Rab2	α_{2B}-AR	58
Rab6	β_2-AR, AT1R, rhodopsin	58–60
Rab8	α_{2B}-AR, β_2-AR, rhodopsin	61–63
Rab26	α_{2A}-AR, α_{2B}-AR	64,65
Rab43	α_{1B}-AR, α_{2A}-AR, α_{2B}-AR, α_{2C}-AR, β_2-AR, AT1R	66
RACK1	TP_β, AT1R, β_2-AR	67
RAMPs	CRLR, CaSR	68,69
RanBP2	Opsin	70
Rap1A	α_{2C}-AR	71
RGGTA	β_2-AR	72
RTPs/REEPs	OR, T2R, α_{2C}-AR	73–75
Sar1	α_{2B}-AR, β_2-AR, AT1R, hCaR, LPA1	76–78
Skb1Hs	SSTR1	79
Syntenin-1	GPR37	80
Tamalin	mGluR1a	81
Tctex-1	Rhodopsin	82
Tubulin	α_{2A}-AR, α_{2B}-AR, AT 1R	83–85
Usp4	A2AR	86
Yif1B	5-HT_{1A}R	29,87

Regulatory proteins: ARF, ADP-ribosylation factor; ATIP1/ATBP50, AT2R-interacting protein 1/AT2R binding protein of 50 kDa; CD74, antigens-associated invariant chain; CLIC4, chloride intracellular channel protein 4; CNIH4, protein cornichon homolog 4; DRiP78, dopamine receptor-interacting protein 78; gC1q-R, receptor for globular “Heads” of c1q; GEC1, glandular epithelial cell 1; GGAs, Golgi-localized, γ-adaptin ear domain homology, ADP ribosylation factor-binding proteins; ARF1-binding proteins; GABARAP, γ-aminobutyric acid receptor-associated protein; Kif5B, kinesin family 5B; MRAP, melanocortin 2 receptor accessory protein; PAPLA1, phosphatidic acid phospholipase A1; PI3K C2A, class II phosphoinositide 3-kinase α; PRAF2, prenylated Rab acceptor family 2; PTEN, phosphatase and tensin homolog; RACK1, receptor for activated C-kinase 1; RAMPs, receptor activity-modifying proteins;

RanBP2, Ran binding protein 2; RGGTA, Rab geranylgeranyltransferase α subunit; RTPs/REEPs, receptor transporting proteins/receptor expression enhancing proteins; Skb1Hs, human sequence of Shk1 kinase-binding protein; Usp4, ubiquitin specific protease 4, Yif1B, Yip1 interacting factor homolog B.

GPCRs: A1AR, A1 adenosine receptor; A2AR, A2 adenosine receptor; AR, adrenergic receptor; AT1R, angiotensin II type 1 receptor; AT2R, angiotensin II type 2 receptor; CaSR, calcium-sensing receptor CCR5, C-C chemokine receptor 5; CRLR, calcitonin receptor-like receptor; CXCR4, C-X-C chemokine receptor 4; DOR, δ-opioid receptor; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; D3R, dopamine D3 receptor; EP3R, prostaglandin EP3 receptor; GABABR, metabotropic γ-aminobutyric acid B receptor; H3R, histamine H3 receptor; hCaR, human calcium-sensing receptor; 5-HT_{1A}R, 5-hydroxytryptamine receptor 1A; 5-HT_{1B}R, 5-hydroxytryptamine receptor 1B; KOR, k-opioid receptor; LPA1, lysophosphatidic acid receptor 1; MCR, melanocortin receptor; mGluR, metabotropic glutamate receptor; MOR, μ-opioid receptor; MR, muscarinic receptor; OR, olfactory receptor; $P2Y_4$R, pyrimidinergic receptor P2Y; PAR, protease-activated receptor; PTHR, parathyroid hormone receptor; SSTR, somatostatin receptor; STR, seven TM receptor; T2R, type 2 taste receptor; TPβ, thromboxane A2 receptor β isoform; V1aR, vasopressin 1a receptor; V2R, vasopressin 2 receptor; VN2R, vomeronasal 2 pheromone receptor.

Table 2.

The interacting proteins of the C-terminus of AT1R

Interacting proteins	Interaction sites	Function	References
β-Arrestin	332–338aa	Internalization, signaling	122
ARAP1	319–359aa	Recycling	123
ATRAP	339–359aa	Internalization	124
Ca^{2+}/CaM	307–320aa	Desensitization	125
Caveolin	YxFxxxxFxxY	ER-Golgi transport	9,10
CD74	Membrane proximal region	ER retention, degradation	12
DRiP78	YxFxxxxFxxY	ER-Golgi transport	9
eNOS	306–325 aa	Signaling	126
GABARAP	Membrane proximal region $F(x)_6LL$	ER-Golgi transport	25,127
GASP	296–359aa	Lysosomal sorting	128
GLP	319–359aa	Signaling	129
G protein	Membrane proximal region	Signaling	118,130
Jak2	YIPP	Signaling	114
PLCγ1	YIPP	Signaling	131
Rab4	Last 10aa	Recycling, phosphorylation	132
Rab5	Last 10aa	Internalization	133
Rab7	Last 10aa	Lysosome transport	132
Rab11	Last 10aa	Recycling	132
Rab43	Helix 8	ER-Golgi transport, sorting	66
SHP-1 and 2	YIPP	Signaling	134
Tubulin	KK	ER-Golgi transport	84

ARAP1, AT1R-associated protein 1; ATRAP, AT1R-associated protein; CaM, calmodulin; eNOS, endothelial nitric oxide synthase; GABARAP, γ-aminobutyric acid receptor-associated protein; GASP, GPCR-associated sorting protein; GLP, GDP/GTP exchange-like protein; PLC, phospholipase C; SHP, Src homology domain 2-containing protein tyrosine phosphatase.