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MINI-REVIEW

New insights into mechanisms of nuclear translocation of G-protein coupled receptors

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ABSTRACT

The G-protein coupled receptor (GPCR) signaling was long believed to involve activation of receptor exclusively at the cell surface, followed by its binding to heterotrimeric G-proteins and arrestins to trigger various intracellular signaling cascades, and termination of signaling by internalization of the receptor. It is now accepted that many GPCRs continue to signal after internalization in the endosomes. Since the breakthrough discoveries of nuclear binding sites for their ligands in 1980s, several GPCRs have been detected at cell nuclei. But mechanisms of nuclear localization of GPCRs, many of whom contain putative nuclear localization signals, remain poorly understood to date. Nevertheless, it is known that subcellular trafficking of GPCRs is regulated by members of Ras superfamily of small GTPases, most notably by Rab and Arf GTPases. In this commentary, we highlight several recent studies which suggest novel roles of small GTPases, importins and sorting nexin proteins in the nuclear translocation of GPCRs via vesicular transport pathways. Taken together with increasing evidence for *in vivo* functionality of the nuclear GPCRs, better understanding of their trafficking will provide valuable clues in cell biology.

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Introduction

Nuclear envelope (NE) is made up of 2 bilayered phospholipid membranes, named outer (ONM) and inner (INM) nuclear membranes. The NE is pierced by multiprotein assemblies, nuclear pore complexes (NPCs), which control trafficking of biomolecules (greater than ~40 kDa) in and out of the nucleus.[1] The ONM is contiguous with outer membrane of endoplasmic reticulum (ER) and the space between 2 nuclear membranes is connected to ER lumen.[1] The basic structure of NPC comprises ~30 nucleoporins forming a ring-shaped central channel with 8 identical subunits.[2] The ultrastructural analysis of NPC reveals that it is made up of distinct classes of nucleoporins; each with specific localization and function. Interestingly, several scaffold nucleoporins, which form the NPC framework, share structural similarities with constituents of COP-II vesicles which are part of endomembrane trafficking pathway.[3] ONM and INM are known to inhabit different transmembrane (TM) proteins, including receptors, ion channels, and linker proteins.[4] The recent evidence suggests that various protein and non-protein components of the NE play diverse roles in regulation of gene expression.[5] The proteomic analysis also shows that the composition of NE varies among tissues.[6]

G-protein coupled receptors (GPCRs), which form the largest family of TM proteins with more than 800 members in the human genome,[7] were believed to be exclusively functional at the plasma membrane (PM). Typically, the heterotrimeric G-proteins act as links between the GPCR at PM and its intracellular second messengers.[8] GPCRs are also well-known to signal via G-protein-independent pathways.[9] Many components of both signaling pathways are found or are translocated at the NE or within the nucleus.[10,11] To date, more than 30 different GPCRs have been localized at the cell nuclei.[11] In addition to GPCRs, TM proteins of the receptor tyrosine kinase (RTK) family have also been detected at the nucleus.[12] The phospholipids in nucleoplasm[13] and the intranuclear invaginations of NE[14] could harbor lipophilic TM domains of these receptors. The

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interactions between various nuclear receptors, including cross-talk between their second messengers, might play a role in the regulation of nuclear signaling cascades.

The origin of nuclear GPCRs

The process of exit of GPCRs from ER requires passing quality control mechanisms and may involve specific motifs present within GPCRs as well as the action of Rab GTPases.[15,16] Because ONM is contiguous with ER membrane, it has been proposed that some resident NE proteins could travel by lateral diffusion.[17,18] However, GPCRs often undergo post-translational modifications in both ER and trans-golgi network (TGN), including glycosylation, which has been implicated in trafficking of various GPCRs to the PM via vesicular transport.[15] The anterograde transport of GPCRs from TGN is also regulated by Rab and Arf GTPases.[19] Based on the immunoblot evidence, PM and nuclear GPCRs have similar molecular weights which is an indirect proof for glycosylation of nuclear GPCRs. This, however, does not rule out presence of an alternative pathway of glycosylation at the nucleus. It has been proposed that synthesis of NE proteins could take place at the nucleus itself.[20] As discussed below, some GPCRs undergo ligand-induced nuclear translocation from PM via importin-regulated trafficking.[21,22] More research is needed to delineate between transport pathways of nuclear GPCRs originating from TGN or PM from those translated locally.

Current evidence for the involvement of small GTPases in localization of NE proteins is limited to Ran GTPase. The vesicular fusion has been a conserved mechanism necessary for reassembly of NE after mitosis in various eukaryotes and the activity of Ran GTPase is required for the process.[23,24] Ran lacks CAAX membrane anchoring motif at its C-terminus, found in other members of Ras superfamily and is primarily involved in nucleocytoplasmic transport along with Karyopherins (discussed below).[25] The Ran GTPase also plays an important role in regulation of cell cycle[26] and in the trafficking of INM resident proteins. Many INM resident proteins contain nuclear localization signal (NLS).[27]

GPCRs and Nuclear localization signal (NLS)

The classical monopartite NLS consists of small cluster of basic amino acids and was originally discovered in the simian virus 40 large-T antigen.[28] The bipartite NLS, on the other hand, consists of 2 clusters of basic amino acids which are separated by 10–12 residues.[29] Both NLSs are recognized by heterodimeric nuclear import receptor, composed of importin α and β. More recently, additional classes of NLSs, binding to different regions of importin α, have been identified.[30] Some of the earliest evidence for the presence of functional NLS in a GPCR was provided for agonist-induced internalization of rat angiotensin II type 1 (Agtr1b) receptor (^{307}KKFKK^{311}) in neurons.[31] In 2003, Lee and colleagues reported that several GPCRs, belonging to Rhodopsin-like receptor family, contain putative NLS which is located just after seventh transmembrane domain. An exception is the apelin receptor which contains a functional NLS in its third intracellular loop.[32] Human formyl peptide receptor 2 (FPR2) has been recently reported to contain a NLS in its 3rd intracellular loop (^{227}KIHKK^{231}) and has been localized at the nuclei in lung and gastric cancer cell lines.[33] Human cysteinyl leukotriene receptor 1 (CYSLTR1) but not CYSLTR2 contains a functional bipartite NLS at its C-terminus.[34] Our group identified presence of 2 monopartite NLS motifs (in first and third intracellular loops, respectively) in human F2R like trypsin receptor 1 (F2RL1), which is a member of protease activated receptor sub-family of class-A GPCRs.[21] The mutational disruption of these motifs revealed that both NLSs are necessary for agonist-induced nuclear translocation of the receptor from PM.[21] We first reported presence of putative monopartite NLS (^{298}KKFRKH^{302}) in the C-terminus of human platelet-activating factor receptor (PTAFR)[35] and recently showed that the NLS is not functional by its mutational disruption.[36] However, internalization motif between 311 and 330 amino acids, present at the C-terminus, is essential for nuclear translocation.[36] It is interesting to note that some GPCR ligands also contain NLS [e.g., parathyroid hormone-related protein].[37] Functional NLS has also been identified as being responsible for nuclear localization of non-GPCR receptors such as erb-b2 receptor tyrosine kinase 2 (also known as HER-2).[38]

NLS and nuclear importins

As described earlier, classical NLSs (monopartite and bipartite) are recognized by the importin-$\alpha.\beta$ heterodimer. Both importins are members of Karyopherin (Kap) family of proteins. Out of 19 human Kapβs, 11 are involved in nuclear import.[39] To date, consensus NLSs have been identified only for importin (Imp) $\alpha.\beta$ (classical NLS) and transportin (PY-NLS) pathways.[39] The PY-NLS consists of weak consensus motifs and physical rules such as structural disorder, overall positive charge, which together identify transportin-mediated nuclear import cargos.[40] The role of importins in nuclear translocation of full-length F2RL1 is further evidenced by RNAi (small interfering RNA) mediated

silencing of Impβ1 (along with Impα3 and Impα5) affecting nuclear localization of the receptor.[21] On the other hand, nuclear import of parathyroid hormone receptor 1 is regulated by its interaction with Impα1 and Impβ.[41] In case of PTAFR, a novel interaction between Rab11a GTPase and importin-5 (Imp5) is essential for nuclear translocation of the receptor.[36] To date, 3 GPCRs, 2 of which belong to chemokine-receptor family (CCR2 and CXCR4 receptors)[42,43] and oxytocin receptor (Oxtr)[22] have been reported to undergo transportin 1 mediated nuclear translocation.

Protein interactions involving Rab GTPases and Importins

The trafficking of GPCRs between various cellular membranes is regulated by small GTPases of the Ras superfamily; especially members of the Rab and Arf families. These small GTPases control various steps of vesicular trafficking including cargo selection, vesicular budding from donor membrane, interaction with cellular motors, and docking of vesicle to the acceptor membrane.[44] Recently, evidence for presence of vesicles in the NE (in the space between ONM and INM) was provided for the nuclear export of herpes viral nucleocaspid[45] and it has been suggested that such a pathway might exist for endogenous TM nuclear proteins as well.[46] Some Rab GTPases link specific intracellular compartments to nuclear signaling via their effector proteins.[47] Others show direct nuclear localization. The latter category includes Rab24 which has been proposed to play a role in NE assembly and/or transport.[48] We found that Rab11a (along with Imp5) plays a role in agonist-independent nuclear translocation of PTAFR.[36] Rab11 effectors (known as family of Rab11 interacting proteins or Rab11 FIPs) are divided into 2 classes based on their sequence homology.[49] class-I FIPs are known to regulate endosomal recycling of TM proteins back to PM; while class-II FIPs participate in the regulation of cell division. class-II FIPs also interact with Arf6 GTPase.[50] Recent evidence suggests that membrane phosphoinositides are involved in recruiting Rab11 effectors to the intracellular membranes.[51] Whether Rab11a is involved directly or indirectly (via one of its effectors) in the nuclear translocation of PTAFR is unknown. Along similar lines, Rab23 has been recently reported to exist in a complex with transportin 1.[52] Finally, several members of Ras and Rho families of small GTPases contain putative NLS.[53] Small GTPases of RGK family are involved in cell shape remodeling by nuclear transport but underlying molecular mechanisms are unknown.[54]

Role of endosomal sorting proteins in nuclear localization of GPCRs

The sortin nexins (SNXs) form another class of evolutionarily conserved eukaryotic proteins which contain Bin/Amphiphysin/Rvs (BAR) and phox homology (PX) domains. These domains are essential for interaction of SNX proteins with various biologic membranes.[55] Recent *in vitro* studies suggest that BAR domain proteins play a role in the regulation of cellular membrane curvature.[56] Snx1 is known to associate with C-terminal tails of many GPCRs.[57] The SNXs were first identified regulators of retromer-dependent endosomal trafficking but current evidence suggests for more diverse roles.[58] Snx6 enhances localization of Lamin-A at the NE.[59] Using confocal microscopy and subcellular fractionation, Zhu and colleagues reported that Snx10 shows nuclear localization in osteoblasts derived from human peripheral blood mononuclear cells as well as from RAW 264.7 mouse cell-line.[60] We found that, Snx11, which lacks BAR domain but contains an extended PX domain and shares the highest sequence homology with Snx10 among the sorting nexin family members, regulates endosomal sorting of F2rl1 (along with aforementioned importins) to the nucleus via trafficking through microtubule network.[21] The extended PX domain of Snx11 is essential for its function *in vivo*.[61] Moreover, it has been proposed that Snx10 contains the extended PX domain, based on its sequence alignment with Snx11.[61]

Arrestins and GPCR trafficking

Roles of β-arrestins in the regulation of endocytic trafficking of agonist-induced phosphorylated GPCRs are reviewed elsewhere.[62] In addition, they can act as effector molecules in non-canonical GPCR signaling.[63] β-arrestins are also known to activate Arf6 GTPase[64] and this process has been shown to control recycling of β2 adrenergic receptor.[65] Out of the 2 non-visual β-arrestins, only β-arrestin1 (arrestin2) shows nuclear localization, where it is involved in histone acetylation and control of gene transcription.[66] β-arrestin2 (arrestin3), on the other hand, is constitutively exported out of the nucleus as it contains leucine-rich nuclear export signal.[67] We found that C-terminal truncated F2rl1 fails to go to the nucleus. However, the mutational disruption of its C-terminal amino acid residues 363 and 366, which are required for arrestin interaction,[68] does not affect agonist-induced nuclear localization of F2rl1.[21] We speculate that agonist-induced binding of some other protein(s) to the C-terminus of F2rl1 might result in the receptor's conformational change to expose its aforementioned NLS motifs. On the other hand, RNAi mediated silencing of

β-arrestin1/2 in osteoblasts has shown that they are required for expression of differentiation-inducing genes in the cells such as osterix (*Sp7*) and bone sialoprotein (*Ibsp*), a function reported to be mediated by nuclear Oxtr.[22] Conversely, mutational disruption of serine-rich clusters in the C-terminus of Oxtr (a common site of GPCR phosphorylation and required for arrestin recruitment) partially impairs its nuclear localization, without affecting the Erk phosphorylation.[22] How arrestin2 regulates Oxtr-induced gene expression in osteoblasts remains to be elucidated. In summary, the role of arrestin2 in governing localization of GPCRs to the nucleus varies according to the GPCR and thus entails additional interacting partners and/or their effect on conformational changes of the complex.

Agonist-dependent vs. -independent nuclear localization of GPCRs

Agonist-dependency for nuclear localization seems to differ according to GPCRs. Following agonist stimulation at the PM, the C-terminus of Frizzled 2 receptor gets cleaved and is translocated to the nucleus by importins (Impβ11 and Impα2).[69] Multiple full-length GPCRs with peptide ligands, such as F2rl1 and Oxtr, also need agonist-induced internalization via one of the endocytic

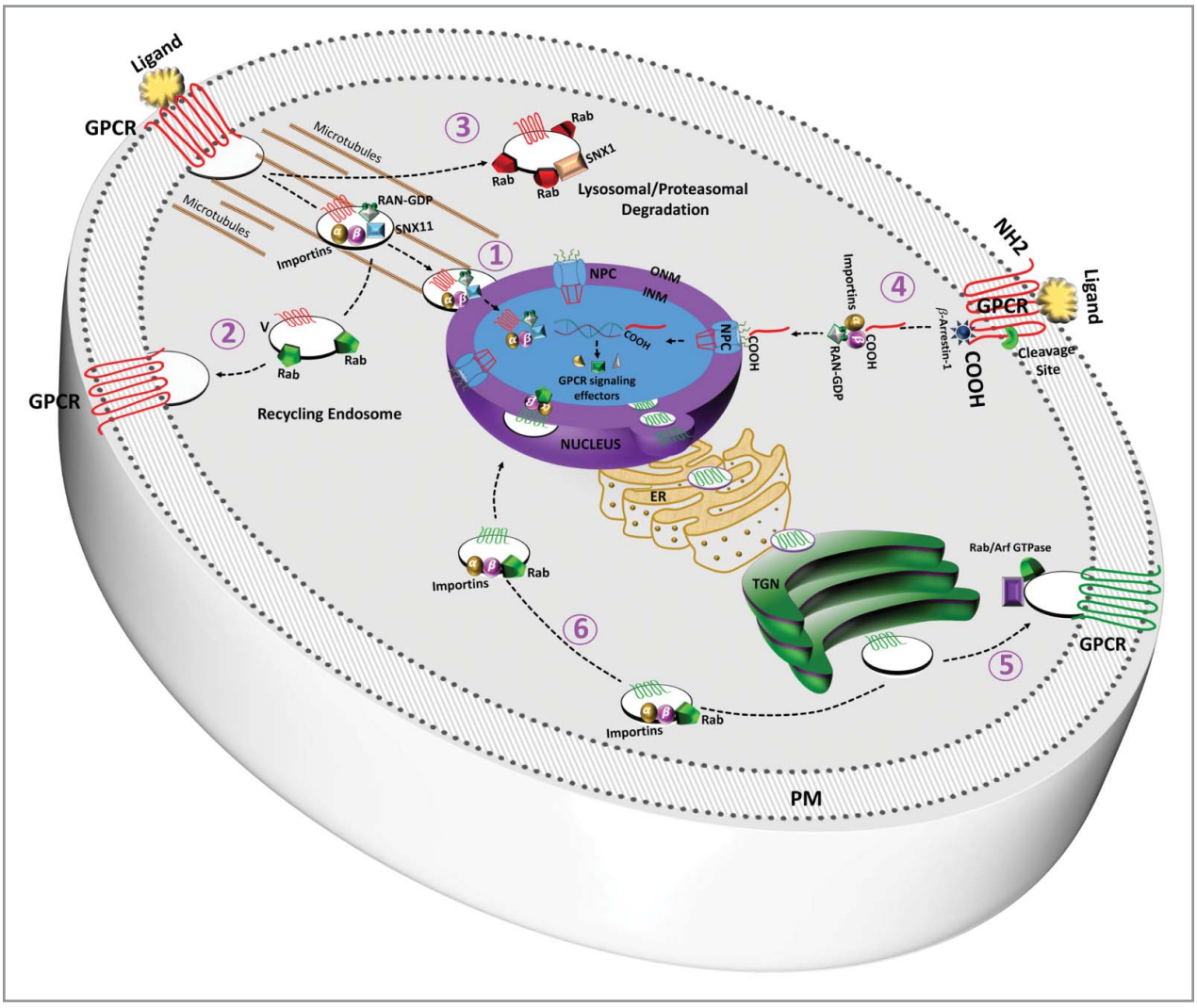

Figure 1. Subcellular GPCR trafficking occurs via vesicular transport mechanisms which are regulated by members of Ras superfamily of small GTPases. Upon binding to its ligand at PM, 1) full-length GPCRs (e.g., F2rl1 and oxytocin receptor) can undergo agonist-induced nuclear translocation by importins and sorting nexins[21,22] or 2) can be recycled back by recycling Rabs (e.g., Rab 4, 11) or 3) targeted for degradation by proteasomes/lysosomes, the process regulated by Rab 7 and sorting nexin 1., 4) In case of the frizzed 2 receptor, its intracellular C-terminus is cleaved off by the action of cellular proteases and only C-terminus is then translocated to nucleus by importins and Ran GTPase.[69] Lastly, agonist-independent translocation of GPCRs directly from TGN 5) and 6) is controlled by rab/arf GTPases and (in case of nuclear translocation 6)) importins as well (Rab11a and importin-5 in case of the platelet-activating factor receptor).[36] More research is needed to understand trafficking of GPCRs between nuclear membranes and their orientation of at the NE.

Table 1. Known mechanisms and receptor motifs required for nuclear translocation of GPCRs.

GPCR	Mechanisms of Translocation and GPCR motifs (if known) required for Nuclear Localization	Endogenous Nuclear Localization	Reference
Adrenoceptors α 1A and 1B	α 1A and 1B receptors contain bipartite and arginine-rich NLS respectively, both within their C-termini.	Adult mouse cardiac myocytes	77
Angiotensin II receptor type 1	The C-terminal monopartite NLS is required for Angiotensin-II induced nuclear translocation of the type-1 receptor in rat neurons and human vascular smooth muscle cells.	Primary rat neurons (hypothalamus and brain stem), human vascular smooth muscle cells	31,78
Apelin receptor	Agonist independent nuclear localization, the receptor contains monopartite NLS in its 3rd intracellular loop.	Human cerebellar and hypothalamic neurons	32
Bradykinin receptor B2	Agonist-independent localization, C-terminal NLS.	Rat hepatocytes	32,71
Chemokine receptors- C-C motif chemokine receptor 2 (CCR2) and C-X-C motif chemokine receptor 4 (CXCR4)	Both receptors undergo transportin 1-mediated nuclear translocation. CXCR4 contains a conserved functional NLS "RPRK" between amino acid residues 146 and 149.	Prostate and renal cancer cell lines (CXCR4)	42,43,79
Cysteinyl leukotriene receptor 1	Bipartite NLS in its C-terminus between residues 310–324.	Colorectal adenocarcinoma cells	34
Endothelin receptor type A and type B	Both Type A and Type B endothelin receptors contain putative NLS in their C-terminus.[32] However; functional role of the motifs hasn't been tested yet.	Human aortic vascular smooth cells, human ventricular endocardial endothelial cells (EECs), rat ventricular cardiomyocytes	80-82
F2R like trypsin receptor 1	Agonist-induced nuclear localization is governed by Snx11, Importins β1, α3 and α5. Both NLS motifs (present in 1st and 3rd intracellular loops) and C-terminus of the receptor are required.	Retinal ganglion neurons (RGC)	21
Formyl peptide receptor 2	Human FPR2 contains a functional NLS in its 3rd intracellular loop between residues 227 and 231.	Lung and gastric cancer cell lines	33
Frizzled receptor 2	C-terminus of drosophila Frizzled 2 receptor gets cleaved after ligand stimulation at PM and is translocated to the nucleus by Impβ11 and Impα2.	Drosophila muscle cells	69,83
Lysophosphatidic acid receptor 1	Agonist-independent. Nuclear localization is regulated by integrin signaling and requires action Rho kinase in PC12 cells.	Piglet brain microvascular endothelial cells, PC12, human bronchial epithelial cells	73,74
Melanocortin 2 receptor (MC2R)	MC2R directly interacts with nucleoporin 50 (NUP50) and Nup50-MC2R complex undergoes agonist-induced nuclear translocation from the PM.	Human adrenocortical epithelial cell-line (H295R)	84
Oxytocin receptor	Agonist-induced nuclear translocation is regulated by transportin 1 and β arrestins.	Primary mouse osteoblasts and MC3T3.E1 preosteoclastic cells	22
Parathyroid hormone receptor 1	The nucleocytoplasmic shuttling is governed by Importins α1 and β.	Rat (ROS 17/2.8) and human (SaOS-2) osteosarcoma cell-lines, mouse pre-osteoblast cell-line (MC3T3-E1)	41
Platelet-activating factor receptor	Nuclear localization is regulated by Rab11a and Importin5. Internalization motif between 311 and 330 residues in C-terminus of the receptor is required. Exogenous stimulation or endogenous agonist production are not needed.	Piglet brain microvascular endothelial cells and human retinal microvascular endothelial cells	35,36
Sphingosine-1-phosphate receptor 1	Agonist-induced translocation	Human umbilical vein endothelial cells	74
VIP and PACAP receptor 1	Exogenous agonist (VIP) stimulation increases nuclear localization VIPR1 but not VIPR2.	Human breast cancer cell-lines (T47D and MDA-MB-468)	70
Glutamate metabotropic receptor 5 (GRM5, previous symbol- mGlu5)	The C-terminus contains a novel NLS between amino acid residues 852 and 876.	Primary rat striatal neurons	87

pathways for their nuclear translocation.[21,22,31] Valdehita and colleagues have shown that exogenous vasoactive intestinal polypeptide increases nuclear localization of vasoactive intestinal peptide receptor 1 (VIPR1, previously known as VPAC1) but not VIPR2 in human breast cancer cell-lines.[70] Others such as apelin receptor and bradykinin receptor B2 have been reported to show agonist-independent nuclear localization.[32,71] However, there have been reports of autocrine apelin signaling in other cellular systems.[72] How endogenous apelin-APJ pathway might affect nuclear translocation of the receptor is unknown. The GPCRs with bioactive lipids as their

ligands, like PTAFR and Lysophosphatidic acid receptor 1 seem to show their nuclear localization is not dependent of agonist stimulation.[35,73] Along these lines, our latest work indicates that exogenous or endogenous ligand (platelet-activating factor) stimulation is not required for nuclear translocation of PTAFR in primary human retinal microvascular endothelial cells.[36] In PC12 cell line, endogenous nuclear localization of lysophosphatidic acid receptor 1 (Lpar1) is regulated by integrin signaling and this has been attributed to the action of Rho family of small GTPases.[74] Whereas sphingosine-1-phosphate receptor 1 (S1PR1) is reported to undergo agonist-induced nuclear translocation in human umbilical vein endothelial cells,[75] issue is further complicated by the fact that most phospholipid ligands can be synthesized locally at the nuclear membranes and these ligands are capable of transversing biomembranes. In case of the PTAFR, its ligand is mainly retained intracellularly in several cell types after synthesis.[76] Current understanding of possible mechanisms of nuclear translocation of GPCRs is summarized in Fig. 1 and Table 1.

Future perspectives

GPCRs are prominent drug targets. It is of critical importance to know the origin and trafficking of nuclear receptors to be able to develop successful pharmacologic strategies to target them. It is improtant to note that in recent years, functional GPCRs have been localized at other intracellular compartments, such as endosomes and mitochondria.[85,86] The charateristic subcellular distribution of small GTPases makes them attractive tools to modify intracellular GPCR trafficking and signaling. Moreover, studying spatio-temporal disctribution and interactions of proteins involved in the GPCR translocation will help to unravel their physiologic roles. These mechanisms appear to be depedent on the type of receptor as well as the cell-type.[11,36] The trafficking of nuclear GPCRs is only part of the puzzle. The recent studies also indicate that nuclear GPCRs perform functions which differ from their plasma membrane counterparts, both *in vitro* and *in vivo*.[21,22,36] New subcellular delivery systems such as nanoparticles might help to better understand the physiologic significance of nuclear GPCRs.[11]

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