The LPA3 Receptor

Subjects: Biology

Contributor: Karina Helivier Solís, Ma. Teresa Romero, Alejandro Guzman Silva, J. Adolfo García-Sáinz

Lysophosphatidic acid receptor 3 (LPA3) is implicated in different physiological and pathological functions through activation of different signal pathways, the result of the regulation process of this receptor. The knowledge of regulating LPA3 could be a crucial element for defined their roles in health and disease.

Keywords: lysophosphatidic acid 3 receptor ; receptor phosphorylation ; lysophosphatidic acid ; PKC ; GRK

1. Introducción

Lysophosphatidic acid (LPA) is a simple lipid comprising a phosphate group and a fatty acid, linked by ester bonds to glycerol residue, which is considered the backbone of this molecule[1][2](**Figure 1**). LPA has a wide distribution in the body. It is found in tissues and fluids, probably due to its chemical and physical characteristics, particularly its low molecular weight and solubility in water[3].

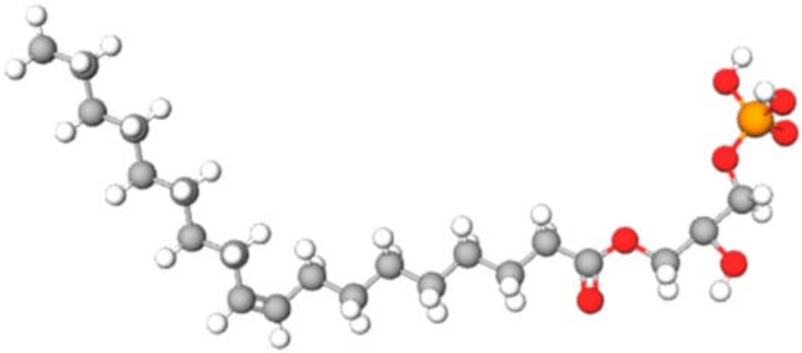

Figura 1. LPA structure. Chemical structure of 1-oleoyl-2-hydroxy-sn-glycerol-3-phosphate (LPA 18: 1). Atoms in the chemical structure: carbon (gray), hydrogen (white), oxygen (red) and phosphorus (orange) https://pubchem.ncbi.nlm.nih.gov/compound/Lysophosphatidic-acid) (https: / /molview.org). Retrieve June 4, 2021.

Two pathways synthesize LPA. In the intracellular pathway, phospholipids (phosphatidylcholine, phosphatidylserine, or phosphatidylethanolamine) or diacylglycerol are the metabolic precursors of LPA through the action of phospholipase D or diacylglycerol kinase, respectively. These enzymes promote the synthesis of phosphatidic acid, which is converted into LPA through catalysis by cytoplasmic lysophospholipases A1 or A2[4][5]. Other molecules from which LPA is synthesized include glycerol-3-phosphate and monoacyl-glycerol. In these processes, we find the participation of the enzymes glycerophosphate acyltransferase and monoacyl-glycerol kinase, respectively[3][6][7].

In the extracellular pathway, LPA is generated from lysophosphatidylcholine, which is found in the extracellular leaflet of plasma membranes or bound to proteins (such as albumin). In this case, secreted lysophospholipases A1 or A2 split a fatty acid from phosphatidylcholine, synthesizing lysophosphatidylcholine, and then converting it into LPA by a phospholipase D, generally denominated Autotaxin[6][8][9].

LPA is degraded by various enzymes, including LPA acyltransferase, which transfers an acyl group from acyl-CoA to LPA, generating phosphatidic acid; LPA lipid phosphatase, which can remove the phosphate group from LPA, generating monoacylglycerol, and lysophospholipases, which lead to the hydrolysis of the acyl group of LPA, producing a free fatty acid and glycerol 3-phosphate[1][2].

LPA is considered a “bioactive lipid”, implying that it, in addition to its role in phospholipid metabolism, regulates a diverse range of cellular and organism responses such as angiogenesis[8][10][11], neuritic retraction[12][13][14], cell migration[15][16], cell proliferation [17][18][19], reorganization of the cytoskeleton[10][20] [10,20], development of the central nervous system[8]

[20][21], neuronal myelination[20][22], pain[23][24], obesity[25], and cancer[26][27][28][29], among many others. These functions are performed by LPA through the activation of six receptors[5][30][31][32][33][34][35].

These receptors are called lysophosphatidic or LPA receptors and are classified into two families. The first family is the lysophospholipid family of receptors, related to those for other phospholipids and including the LPA_1, LPA_2, and LPA_3 receptors. The second family is phylogenetically related to the purinergic receptors and includes the LPA_4, LPA_5, and LPA_6 receptors[1][3][8][36].

These LPA receptors belong to the G protein-coupled receptor (GPCR) superfamily. They are structurally constituted of seven transmembrane hydrophobic domains connected by three intracellular loops and three extracellular loops, with an extracellular amino-terminal group and an intracellular carboxyl terminus. According to the classification criteria in the GRAFS (Glutamate, Rhodopsin, Adhesion, Frizzled/Taste2, and Secretin groups) system[37] and in the AF system, all of these receptors belong to family A[37][38][39]. These receptors are associated for their signaling with heterotrimeric GTPases or “G” proteins. LPA receptors can activate different Gα proteins ($G\alpha_{q/11}$ $G\alpha_{i/o}$, $G\alpha_{12/13}$, $G\alpha_s$); some of these receptors are considered promiscuous because they can activate different G proteins and downstream signaling pathways that regulate various physiological functions as well as being involved in the pathogenesis of different diseases[5][38][39] (**Figure 2**).

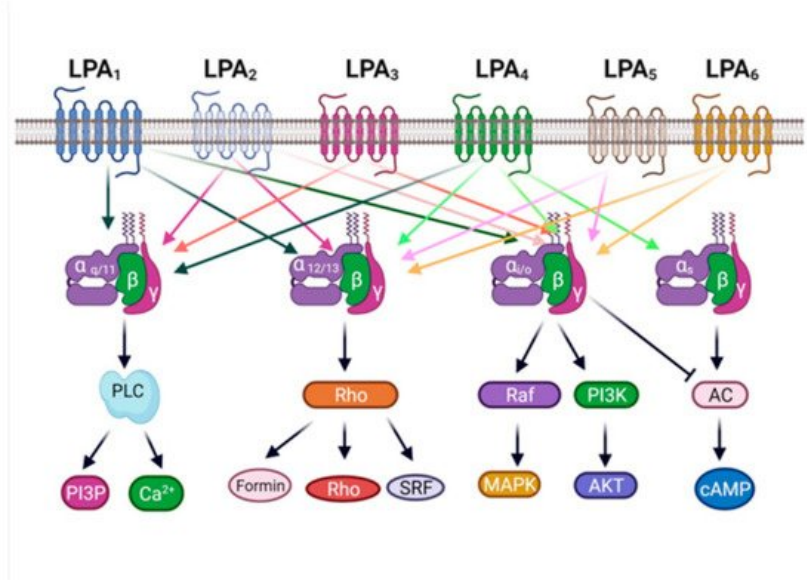

Figure 2. LPA receptors and G proteins. LPA receptors couple with different G proteins that activate distinct signaling pathways. PLC, phospholipase C; PI3K. phosphoinositide 3-kinase; AC, adenylyl cyclase. Created with BioRender.com.

The activation of GPCRs by their agonists leads to conformational changes promoting heterotrimeric G protein interaction and the exchange of GDP for GTP in their G_α subunits, favoring the dissociation of these heterotrimeric proteins into their G_α subunits, and the βγ complexes, which separately mediate the activation of downstream proteins[8][40][41]. The termination/attenuation of signaling is associated with receptor phosphorylation by different protein kinases (including G protein-coupled receptor kinases (GRKs) and second messenger-activated kinases, among others)[42][43][44][45][46][47][48][49][50]. Such phosphorylations facilitate interaction with β-arrestins, disfavoring receptor-G protein interaction (therefore, decreasing G protein-mediated signaling), recruiting the endocytic machinery, promoting receptor internalization (**Figure 3**), and activating alternative signaling processes[49][50][51][52][53].

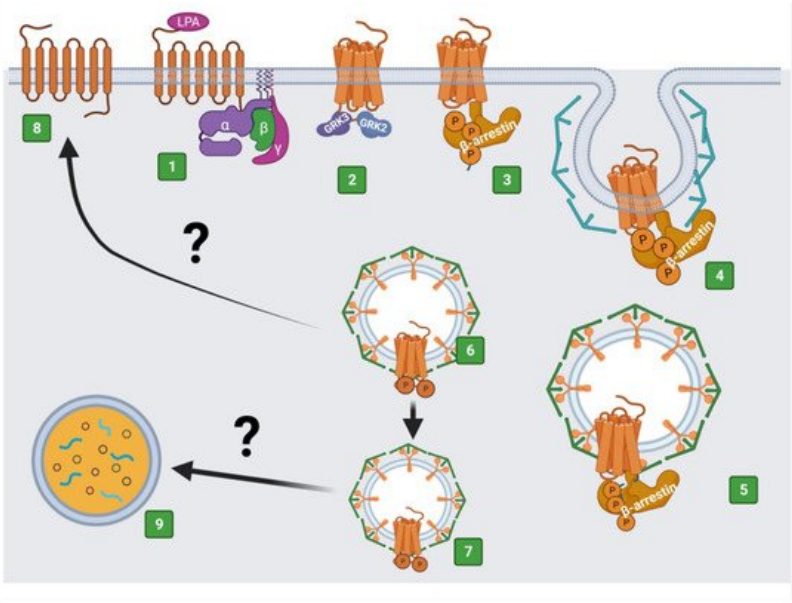

Figure 3. Internalization of agonist-activated LPA_3 receptors. (1) Activation of LPA_3 with LPA and recruitment of a G protein. (2) Exposure of GPCR phosphorylation sites. (3) Recruitment of β-arrestin through interaction with phosphorylated sites. (4) Recruitment of the endocytic machinery that initiates receptor endocytosis. (5) Endocytosis of LPA_3 via endosomes. (6) Receptor-endosomal traffic to (7) lysosomal receptor degradation or (8) receptor recycling to the plasma membrane. Question marks indicate that there is little information on these processes, which are postulated in similarity to what has been defined for other receptors. Created with BioRender.

As indicated, the LPA receptors belonging to the lysophospholipid family include the LPA_{1-3} receptors. These receptors have been studied in more detail (reviewed in[8][9]). The LPA_1 receptor is a 364 amino acid protein, which interacts mainly with $G_{i/o}$, $G_{q/11}$, and $G_{12/13}$. In mice, knocking out the expression of this receptor subtype markedly affects the development of the central nervous system and decreases survival (50% perinatal death). Alteration of LPA_1 expression has been associated with cancer, neuropathic pain, and fibrosis of the lungs. LPA_2 is a protein of 348 amino acid residues that interacts with $G_{i/o}$, $G_{q/11}$, and $G_{12/13}$. Constitutive receptor loss in mice produces an essentially normal phenotype; however, this receptor contributes to the development and function of synapsis in embryos and adult mice. It has also been associated with some types of cancer and lung functional alterations, such as asthma. The LPA_3 receptor is a GPCR whose activation mainly promotes the recruitment of two G proteins: $G\alpha_{q/11}$ and $G\alpha_{i/o}$; therefore, it is considered promiscuous. The LPA_3 receptor regulates different signal pathways, as depicted in **Figure 4**. It should be mentioned that LPA receptors (LPA_{1-3} form homo- and heterodimers within the subgroup and heterodimers with other receptors such as those of the sphingosine 1-phosphate receptor ($S1P_{1–3}$) and the proton-sensing GPCR, GPR4[54]. This adds a new level of complexity in signaling and regulation, which we consider important to mention, but it is not considered in the present review.

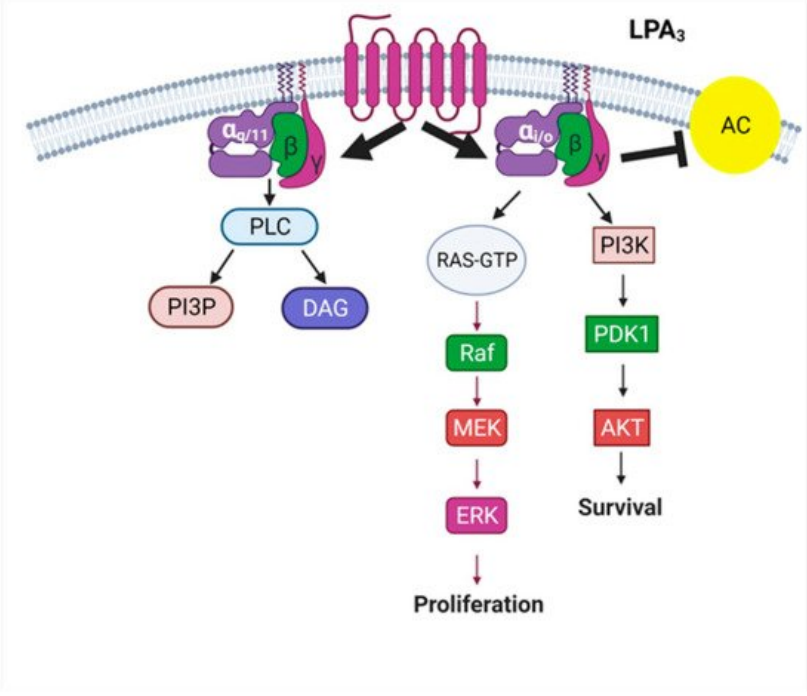

Figure 4. Signaling pathway of LPA_3 receptors. Activation of this receptor subtype with LPA promotes conformational changes favoring intense interaction with $G_{\alpha q/11}$ and $G_{\alpha i/o,}$ which lead to activation of downstream signaling molecular entities. Abbreviations as in **Figure 2**. Created with BioRender.

2. The LPA_3 Receptor: Structure and Function

The human LPA_3 receptor (https://www.uniprot.org/uniprot/Q9UBY5; Accessed on 12 May 2021) is constituted of 353 amino acids (mouse and rat orthologs, 354 amino acids), and its calculated molecular weight is ≈40 KDa (39,998 Da)[5][55][56]. As previously indicated, according to the classification systems GRAFS and A-F, this receptor belongs to the A family[36][37]. LPA_3 is mainly coupled to two G proteins, $G\alpha_{q/11}$ and $G\alpha_{i/o}$; therefore, the G protein-binding motif of this receptor subtype is considered promiscuous. This property allows this receptor to activate different signal pathways, which might explain why it does participate in a large variety of physiological functions and, as previously mentioned, in the pathogenesis of diseases[5][8][57].

As a member of the GPCR superfamily, the LPA_3 receptor is constituted of seven hydrophobic transmembrane domains (TM), which are joined through three extracellular and three intracellular loops (**Figure 5**). It is worth mentioning that transmembrane regions are essential for this receptor, as has been observed for others that also belong to the A family. These regions or domains are frequently conserved[58].

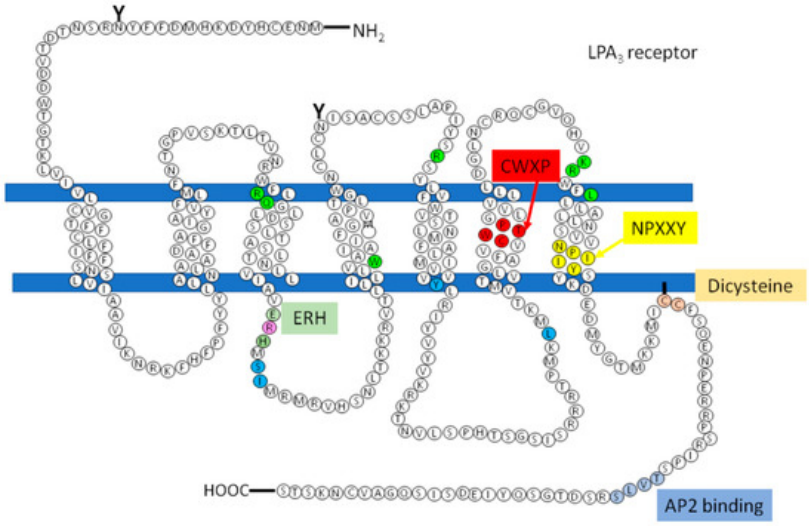

Figure 5. LPA_3 receptor structure, domains and sites that regulate this receptor. Image shows the amino acid sequence and the organization of the LPA_3 receptor with three extracellular loops, three intracellular loops, the seven transmembrane domains, the extracellular amino terminus (-NH_2), and the intracellular carboxyl terminus (-COOH). Colored boxes indicate conserved motifs putatively relevant for activation and regulation of the LPA_3 receptor. Putative sites where LPA interacts with LPA_3 are shown in green, while proposed places where GPCRs could be recruiting G proteins are marked in blue and purple (R, arginine that is also part of the ERH motif). "Y" indicates a potential glycosylation site, and the line joining one of the cysteines to the membrane is a putative palmitoylation site.

Available information on LPA_3 receptor structure/function is scarce. Therefore, in order to obtain some information, we performed *in silico* analyses. This allowed us to identify different domains observed in other GPCRs. Among these are the following: an ERH (Glutamic acid-Arginine-Intrahelical hydrogen bonding residue) domain (analogous to the DRY (Aspartic acid-Arginine-Tyrosine) motif) in the transition between the end of TM3 and the initiation of ICL2, a CWXP domain within TM6, an NPXXY domain near the end of TM7, and a di-cysteine domain within the carboxyl terminus (**Figure 5**). Studies on these domains in other receptors have shown that they are important for the activation and regulation of the GPCRs receptors of the A family[59][60][61][62]. Additionally, an AP2-binding domain is present in the carboxyl terminus[62][63][64].

It is noteworthy to mention that the mutation of these domains usually reduces or abolishes agonist-activation of GPCRs. Studies employing molecular docking showed that ligand binding at GPCRs produced the packaging of TM3-5-6-7 domains; this event was promoted by destabilization of an ionic interaction[60][65], initiating a displacement of TM7 toward TM3 and promoting activation involving the tyrosine residue present in the DRY motif, which is associated with the rotation of the cytoplasmic extreme of TM6 and which promotes the activation of these receptors[60][66][67][68][69].

Additionally, the asparagine residue of the NPXXY motif establishes interactions with other residues, facilitating the movement of TM7 toward TM3[60][67] and promoting the stability of the activated receptor. Finally, the DRY motif forms a salt bridge with surrounding residues and with TM6; this salt bridge breaks at the moment the ligand binds. The DRY motif creates a new interaction with TM5, stabilizing the receptor in its active conformation, breaking contacts between TM3 and TM6, thus promoting a movement toward the cellular cytoplasm of TM6, which increases the receptor binding to the G_{α} protein. These events initiate signaling, favor receptor phosphorylation, and later favor association with β-arrestins, all of which are relevant for receptor desensitization[53][60][67][68][69].

The CWXP domain is a motif found in TM6 which seems to participate in the binding of agonists. Rotation of the tryptophan residue causes movements within the binding pocket, promoting the accommodation of the ligand into the receptor. In contrast, the proline residue induces a bend that serves as a pivot for helical movement during receptor activation[60][61][67][68][69][70]. Other motifs that appear to participate in the activation of GPCRs include the PIF (GPCR microswitch; Proline-Isoleucine-Phenylalanine) motif that is usually found in TM4 and the NPXXY motif found in TM7, both of which are also related to the activation of $G\alpha_q$, $G\alpha_s$, $G\alpha_i$ and β-arrestins[67][71][72][73][74]. It has been shown that in some receptors (such as the histamine 2 receptor[74][75], the formyl peptide receptor[47][68][75], and α- and β-adrenoceptors[61][76], among others), this domain could be regulating agonist-induced internalization, which affects MAPK pathway activation and intracellular calcium mobilization.

The majority of the motifs that generally regulate the activation of GPCRs, including those in the LPA_1 receptor, have also been found in the LPA_3 receptor (**Figure 5**). Only the PIF domain could not be found in the receptor sequence. Therefore, it appears likely that other receptor region(s) could replace the role of PIF in receptor activation.

This illustrates the putative importance of the motifs present in the LPA_3 receptor at the time of its activation when the ligand binds to it; however, we must recall that the intracellular loops and the carboxyl-terminal region play essential roles, particularly in receptor desensitization and internalization. Current ideas suggest key roles in the phosphorylation of specific residues, mediated by GRKs, second messenger-activated, and other protein kinases[68][77][78].

Other important regions of the LPA_3 structure are the transmembrane domains, which contain residues that take part in ligand binding. It is worth mentioning that the LPA receptors that belong to the lysophospholipid subfamily entertain an ≈81% similarity among themselves[79][80].

Few studies have reported the participation of these residues during the binding of the ligand in LPA receptors. The residues where LPA has been shown to interact with LPA receptors include arginine 105, glutamine 106, tryptophan 153, arginine 185, lysine 279, and arginine 276 (**Figure 5**, residues in green). These sites are conserved in the LPA_1, LPA_2, and LPA_3 receptors, but differences appear to exist between these[5][55][57][79][80]. In the case of tryptophan 153, when it was mutated to alanine in the LPA_3 receptor, it induced a decrease in the potency and efficacy of LPA; such changes were not observed when the LPA_1 and LPA_2 receptors were similarly mutated. Likewise, when arginine 279 was substituted with alanine, a decrease in the activation of LPA_1 and LPA_2, but not in the LPA_3 receptor, was observed[79][80].

Another structure important is an amphipathic α-helix, frequently denominated helix 8, that maintains the F (R/K) XX (F/L) XXX (L/F)sequence that is conserved in GPCRs of the A family and has been reported to participate in the maintenance of the receptor on the cell surface promoting GPCR trafficking, and participating in the activation of the G proteins and the receptor's interaction with the β-arrestins[81][82][83][84].

However, there are receptors of the same family that do not present this sequence that could be involved in the recruitment of the G protein, how is the LPA_3, so according to studies carried out by Zhou and coworkers, in which it is proposed that in response to agonist-induced conformational changes, residues in transmembrane domains 3, 5, and 6 interact with and activate G proteins[77]. These residues were found in the structure of the LPA_3 receptor as shown in **Figure 5** (indicated in cerulean).

The GRKs are a family of protein kinases that appears to play a major role in the phosphorylation of agonist-occupied GPCRs (**Table 1**). This family is made up of seven different isoforms that are constituted of a central catalytic domain which is conserved in all GRKs; an amino-terminal area and the carboxyl terminus, both of which differ among these protein kinases, seem to confer them selectivity in their action, and participate in their regulation. These domains constitute the structural basis for their classification into subfamilies; in addition, some GRKs exhibit selective expression in some tissues[85][86][87][88]. The visual GRKs (GRK1 and GRK7) are mainly expressed in the retina, GRK4 is mainly expressed in the testis, whereas the other GRKs (2, 3, 5, and 6) are ubiquitously expressed; visual GRKs have short prenylation sequences (see reviews in[85][88] and references therein). The second subfamily, denominated GRK2 and also, for historical reasons, the β-adrenergic receptor kinase (or βARK) subfamily, exhibits a Pleckstrin homology domain that

interacts with G protein βγ dimers and phosphatidylinositol 4, 5-bisphosphate. These kinases are cytoplasmic and their interaction with the plasma membrane seems to occur through these domains. The GRK4 subfamily seems to be bound to the plasma membrane through palmitoylation and/or the presence of positively charged lipid-binding elements[85][86][87][88]. It has been proposed that lipids covalently bound to the carboxyl terminus of these proteins, the Pleckstrin homology domain that associates with phosphoinositides, and the polybasic/hydrophobic regions permit these kinases to be recruited to the membrane and to catalyze GPCR phosphorylation at specific residues[87][88][89][90][91].

Table 1. GRKs that putatively phosphorylate different sites in GPCRs.

Subfamilies	GRKs	Domains of Interest
Visual GRKs	**GRK1 and GRK7**	**Prenylation**
GRK2 or βARK	**GRK2 and GRK3**	**Pleckstrin homology**
GRK4	**GRK4, GRK5 and GRK6**	**Palmitoylation, polybasic hydrophobic domains**

Such specificity in the GPCR phosphorylation pattern appears to be critical to define subsequent signaling (frequently associated with β-arrestin activation), vesicular trafficking, and the receptor's fate (rapid or slow recycling to the plasma membrane, or degradation). This has been named the "GPCR phosphorylation barcode," and numerous research groups are actively working to understand (i.e., to break) this code, which currently is only partially understood[46][50][92][93][94][95][96]. Obviously, initial steps include knowing that the GPCR of interest is actually phosphorylated, the conditions under which that takes place, and the definition of the specific sites affected by such covalent modification. At present, there is evidence that LPA_3 receptors are phosphorylated in response to agonists and other agents (associated respectively with homologous and heterologous desensitizations)[46][57]. However, to date, the phosphorylation pattern(s) of this receptor is (are) unknown, which seems to be an important gap in our knowledge.

Studies conducted *in silico* showed that the LPA_3 receptor can be phosphorylated by different protein kinases[57]. Not surprisingly, different isoforms of GRK and PKC are predicted to be responsible for many such phosphorylations; however, other protein kinases such as PKA, PKB/AKT, and some protein tyrosine kinases were present in this *in silico* analysis [97]. Many of these predicted phosphorylation sites could be targeted by several protein kinases[57][97].

Considering the vital role that GRKs play in homologous desensitization/phosphorylation, the putative sites for the action of this family of kinases on LPA_3 receptor phosphorylation are presented in **Figure 6**. These residues were obtained in a new analysis employing different and/or updated software programs, including GPS5 (http://gps.biocuckoo.cn; Accessed on 3 April 2021), netphorest (http://netphorest.info; Accessed on 3 April 2021), quokka (https://quokka.erc; Accessed on 4 April 2021) and NetPhos 3.1 (http://www.cbs.dtu.dk; Accessed on 4 April 2021). The criterion used to carry out each study was a high threshold. Only residues that were putative targets of GRK, PKA, or PKC and that obtained a high score were considered. Subsequently, we carried out an analysis on the results obtained and chose the residues that were consistently observed in these analyses; these are presented in **Figure 6**. The majority of the GRK putative phosphorylation-target residues were found in intracellular loop 3 and the carboxyl terminus region. Not surprisingly, the different software programs used suggested roles of isoforms of the GRK2 and GRK4 subfamilies (**Table 1**).

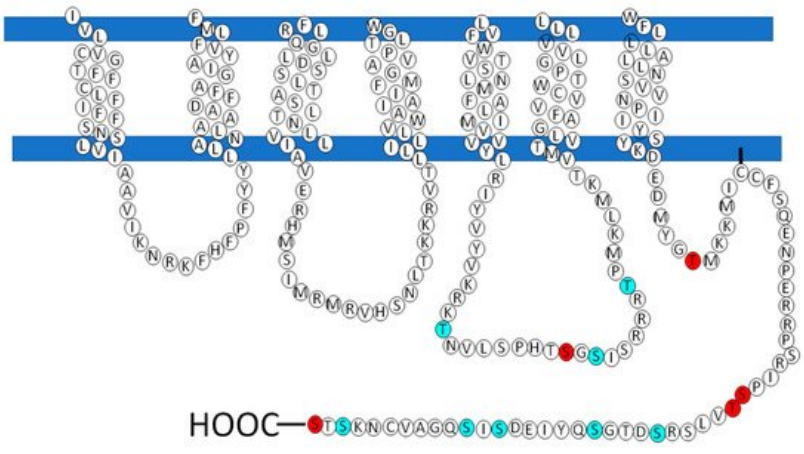

Figure 6. *In silico* prediction of serine and threonine sites phosphorylated by GRK, PKA and PKC. LPA_3 structure is represented, showing (in red) the putative sites targeted by GRK and (in cerulean) putative sites phosphorylated by PKA or PKC.

The possibility that different GRK isoforms may participate in LPA_3 phosphorylation is provocative. It has been proposed that GRK 2 and 3 promote receptor endocytosis by the β-arrestin/clathrin pathway more efficiently than other isoforms. At the same time, GRK 5 and 6 appear to mediate β-arrestin-triggered ERK 1/2 signaling[98][85][87][93][85][99][100][101][102]. It is important to mention that GRKs, in addition to carrying out GPCR phosphorylation, can phosphorylate other proteins in the cell cytoplasm that are involved in cell signaling, as well as receptor trafficking proteins such as $G_{\alpha q}$ and $G_{\beta\gamma}$, PI3K, clathrin, caveolin, MEK, and AKT/PKB, among others[91][92][103][104][105][106][107][108].

It is noteworthy that the *in silico* analysis suggested that PKA and PKC could participate in LPA_3 receptor phosphorylation (**Figure 6** and **Table 2**); this result is of interest because it might indicate the involvement of these protein kinases in the heterologous desensitization of this receptor. It has been reported previously that LPA_{1-3} receptors can be phosphorylated in response to the pharmacological activation of PCK with phorbol myristate acetate[57]. However, to the extent of our knowledge, there is no evidence of PKA-induced LPA_3 receptor phosphorylation. It should be noted that the *in silico.* Detailed analysis shows a marked overlap between GRK, PKA and PKC, suggesting that some sites could be the target of these clusters of kinases. (**Tabla 1** y **Tabla 2**).

Tabla 2. In silico prediction of residues of LPA_3 phosphorylated by PKC and PKA.

Posición	Aminoácidos	PKC / PKA
130	S	PKA
217	T	PKCα / PKCδ / PKCγ
233	T	PKA / PKCδ / PKCι / PKCζ
243	T	PKCi / PKCζ
321	S	PKA / PKCδ /
325	S	PKA / PKC / PKCε
341	S	PKCε
351	S	PKCε

References

1. Yasuyuki Kihara; Michael Maceyka; Sarah Spiegel; Jerold Chun; Lysophospholipid receptor nomenclature review: IUPHAR Review 8. *Journal of Cerebral Blood Flow & Metabolism* **2014**, *171*, 3575-3594, 10.1111/bph.12678.
2. Fang Yang; Guo-Xun Chen; Production of extracellular lysophosphatidic acid in the regulation of adipocyte functions and liver fibrosis.. *World Journal of Gastroenterology* **2018**, *24*, 4132-4151, 10.3748/wjg.v24.i36.4132.
3. Frédérique Gaits; Olivier Fourcade; François Le Balle; Geneviève Gueguen; Bernadette Gaigé; Ama Gassama-Diagne; Josette Fauvel; Jean-Pierre Salles; Gérard Mauco; Marie-Françoise Simon; et al. Lysophosphatidic acid as a phospholipid mediator: pathways of synthesis.. *FEBS Letters* **1997**, *410*, 54-58, 10.1016/s0014-5793(97)00411-0.
4. Keita Nakanaga; Kotaro Hama; Junken Aoki; Autotaxin--an LPA producing enzyme with diverse functions. *The Journal of Biochemistry* **2010**, *148*, 13-24, 10.1093/jb/mvq052.
5. Yun C. Yung; Nicole C. Stoddard; Jerold Chun; LPA receptor signaling: pharmacology, physiology, and pathophysiology. *Journal of Lipid Research* **2014**, *55*, 1192-1214, 10.1194/jlr.r046458.
6. Junken Aoki; Mechanisms of lysophosphatidic acid production. *Seminars in Cell & Developmental Biology* **2004**, *15*, 477-489, 10.1016/j.semcdb.2004.05.001.
7. Sindhu Ramesh; Manoj Govindarajulu; Vishnu Suppiramaniam; Timothy Moore; Muralikrishnan Dhanasekaran; Autotaxin–Lysophosphatidic Acid Signaling in Alzheimer's Disease. *International Journal of Molecular Sciences* **2018**, *19*, 1827, 10.3390/ijms19071827.
8. Ji Woong Choi; Deron R. Herr; Kyoko Noguchi; Yun C. Yung; Chang-Wook Lee; Tetsuji Mutoh; Mu-En Lin; Siew T. Teo; Kristine E. Park; Alycia N. Mosley; et al. LPA Receptors: Subtypes and Biological Actions. *Annual Review of Pharmacology and Toxicology* **2010**, *50*, 157-186, 10.1146/annurev.pharmtox.010909.105753.
9. Jerold Chun; Timothy Hla; Kevin R. Lynch; Sarah Spiegel; Wouter H. Moolenaar; International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid Receptor Nomenclature: TABLE 1. *Pharmacological Reviews* **2010**, *62*, 579-587, 10.1124/pr.110.003111.

10. Daisuke Yasuda; Daiki Kobayashi; Noriyuki Akahoshi; Takayo Ohto-Nakanishi; Kazuaki Yoshioka; Yoh Takuwa; Seiya Mizuno; Satoru Takahashi; Satoshi Ishii; Lysophosphatidic acid–induced YAP/TAZ activation promotes developmental angiogenesis by repressing Notch ligand Dll4. *Journal of Clinical Investigation* **2019**, *129*, 4332-4349, 10.1172/jci121955.

11. Carol M. Rivera-Lopez; Amy L. Tucker; Kevin R. Lynch; Lysophosphatidic acid (LPA) and angiogenesis. *Angiogenesis* **2008**, *11*, 301-310, 10.1007/s10456-008-9113-5.

12. Isabel Gross; Anja U. Bräuer; Modulation of lysophosphatidic acid (LPA) receptor activity: the key to successful neural regeneration?. *Neural Regeneration Research* **2019**, *15*, 53-54, 10.4103/1673-5374.264452.

13. C. Laura Sayas; M. Teresa Moreno-Flores; Jesús Avila; Francisco Wandosell; The Neurite Retraction Induced by Lysophosphatidic Acid Increases Alzheimer's Disease-like Tau Phosphorylation. *Journal of Biological Chemistry* **1999**, *274*, 37046-37052, 10.1074/jbc.274.52.37046.

14. Jong Hee Choi; Minhee Jang; Yeeun Jang; Ik Hyun Cho; Gintonin, a ginseng-derived ingredient, as a novel therapeutic strategy for Huntington's disease: Activation of the Nrf2 pathway through lysophosphatidic acid receptors. *IBRO Reports* **2019**, *6*, S101, 10.1016/j.ibror.2019.07.327.

15. Eriko Tanabe; Misaho Kitayoshi; Kyohei Yoshikawa; Ayano Shibata; Kanya Honoki; Nobuyuki Fukushima; Toshifumi Tsujiuchi; Loss of lysophosphatidic acid receptor-3 suppresses cell migration activity of human sarcoma cells. *Journal of Receptors and Signal Transduction* **2012**, *32*, 328-334, 10.3109/10799893.2012.738689.

16. Kyoko Okabe; Kohei Kato; Miki Teranishi; Mai Okumura; Rie Fukui; Toshio Mori; Nobuyuki Fukushima; Toshifumi Tsujiuchi; Induction of lysophosphatidic acid receptor-3 by 12-O-tetradecanoylphorbol-13-acetate stimulates cell migration of rat liver cells. *Cancer Letters* **2011**, *309*, 236-242, 10.1016/j.canlet.2011.06.020.

17. Shinya Shano; Kazuki Hatanaka; Shinsuke Ninose; Ryutaro Moriyama; Toshifumi Tsujiuchi; Nobuyuki Fukushima; A lysophosphatidic acid receptor lacking the PDZ-binding domain is constitutively active and stimulates cell proliferation. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* **2008**, *1783*, 748-759, 10.1016/j.bbamcr.2007.11.013.

18. Mai Hayashi; Kyoko Okabe; Kohei Kato; Mai Okumura; Rie Fukui; Nobuyuki Fukushima; Toshifumi Tsujiuchi; Differential function of lysophosphatidic acid receptors in cell proliferation and migration of neuroblastoma cells. *Cancer Letters* **2012**, *316*, 91-96, 10.1016/j.canlet.2011.10.030.

19. Zachariah G. Goldsmith; Ji Hee Ha; Muralidharan Jayaraman; Danny N. Dhanasekaran; Lysophosphatidic Acid Stimulates the Proliferation of Ovarian Cancer Cells via the gep Proto-Oncogene G 12. *Genes & Cancer* **2011**, *2*, 563-575, 10.1177/1947601911419362.

20. Brigitte Anliker; Ji Woong Choi; Mu-En Lin; Shannon E. Gardell; Richard R. Rivera; Grace Kennedy; Jerold Chun; Lysophosphatidic acid (LPA) and its receptor, LPA1, influence embryonic schwann cell migration, myelination, and cell-to-axon segregation. *Glia* **2013**, *61*, 2009-2022, 10.1002/glia.22572.

21. Laura Sánchez-Marín; David Ladrón de Guevara-Miranda; M. Carmen Mañas-Padilla; Francisco Alén; Román D. Moreno-Fernández; Caridad Díaz-Navarro; José Pérez-Del Palacio; María García-Fernández; Carmen Pedraza; Francisco J. Pavón; et al. Systemic blockade of LPA1/3 lysophosphatidic acid receptors by ki16425 modulates the effects of ethanol on the brain and behavior. *Neuropharmacology* **2018**, *133*, 189-201, 10.1016/j.neuropharm.2018.01.033.

22. Yun C. Yung; Nicole C. Stoddard; Hope Mirendil; Jerold Chun; Lysophosphatidic Acid Signaling in the Nervous System. *Neuron* **2015**, *86*, 341, 10.1016/j.neuron.2015.03.043.

23. Hiroshi Ueda; Hiroyuki Neyama; Keita Sasaki; Chiho Miyama; Ryusei Iwamoto; Lysophosphatidic acid LPA1 and LPA3 receptors play roles in the maintenance of late tissue plasminogen activator-induced central poststroke pain in mice. *Neurobiology of Pain* **2018**, *5*, 100020, 10.1016/j.ynpai.2018.07.001.

24. Ken Kuwajima; Masahiko Sumitani; Makoto Kurano; Kuniyuki Kano; Masako Nishikawa; Baasanjav Uranbileg; Rikuhei Tsuchida; Toru Ogata; Junken Aoki; Yutaka Yatomi; et al. Lysophosphatidic acid is associated with neuropathic pain intensity in humans: An exploratory study. *PLOS ONE* **2018**, *13*, e0207310, 10.1371/journal.pone.0207310.

25. Susann Fayyaz; Lukasz Japtok; Fabian Schumacher; Dominik Wigger; Tim Julius Schulz; Kathrin Haubold; Erich Gulbins; Heinz Völler; Burkhard Kleuser; Lysophosphatidic Acid Inhibits Insulin Signaling in Primary Rat Hepatocytes via the LPA3 Receptor Subtype and is Increased in Obesity.. *Cellular Physiology and Biochemistry* **2017**, *43*, 445-456, 10.1159/000480470.

26. Gábor Tigyi; Mélanie A. Dacheux; Kuan-Hung Lin; Junming Yue; Derek Norman; Zoltán Benyó; Sue Chin Lee; Anti-cancer strategies targeting the autotaxin-lysophosphatidic acid receptor axis: is there a path forward?. *Cancer and Metastasis Reviews* **2021**, *40*, 3-5, 10.1007/s10555-021-09955-5.

27. Kai Sun; Hui Cai; Xiaoyi Duan; Ya Yang; Min Li; Jingkun Qu; Xu Zhang; Jiansheng Wang; Aberrant expression and potential therapeutic target of lysophosphatidic acid receptor 3 in triple-negative breast cancers. *Clinical and*

Experimental Medicine **2014**, *15*, 371-380, 10.1007/s10238-014-0306-5.

28. Ming Quan; Jiu-Jie Cui; Xiao Feng; Qian Huang; The critical role and potential target of the autotaxin/lysophosphatidate axis in pancreatic cancer. *Tumor Biology* **2017**, *39*, 1-11, 10.1177/1010428317694544.
29. Jiang Chen; Hongyu Li; Wenda Xu; Xiaozhong Guo; Evaluation of serum ATX and LPA as potential diagnostic biomarkers in patients with pancreatic cancer. *BMC Gastroenterology* **2021**, *21*, 1-10, 10.1186/s12876-021-01635-6.
30. Jong Han Lee; Donghee Kim; Yoon Sin Oh; Hee-Sook Jun; Lysophosphatidic Acid Signaling in Diabetic Nephropathy.. *International Journal of Molecular Sciences* **2019**, *20*, 2850, 10.3390/ijms20112850.
31. G Tigyi; R Miledi; Lysophosphatidates bound to serum albumin activate membrane currents in Xenopus oocytes and neurite retraction in PC12 pheochromocytoma cells.. *Journal of Biological Chemistry* **1992**, *267*, 21360-21367, 10.1016/s0021-9258(19)36618-9.
32. Elisabeth Panther; Marco Idzko; Silvia Corinti; Davide Ferrari; Yared Herouy; Maja Mockenhaupt; Stefan Dichmann; Peter Gebicke-Haerter; Francesco Di Virgilio; Giampiero Girolomoni; et al. The Influence of Lysophosphatidic Acid on the Functions of Human Dendritic Cells. *The Journal of Immunology* **2002**, *169*, 4129-4135, 10.4049/jimmunol.169.8.4129.
33. Jeremy D. Ward; Danny N. Dhanasekaran; LPA Stimulates the Phosphorylation of p130Cas via G i2 in Ovarian Cancer Cells. *Genes & Cancer* **2012**, *3*, 578-591, 10.1177/1947601913475360.
34. Jinjing Yang; Jiyao Xu; Xuebin Han; Hao Wang; Yuean Zhang; Jin Dong; Yongzhi Deng; Jingping Wang; Lysophosphatidic Acid Is Associated With Cardiac Dysfunction and Hypertrophy by Suppressing Autophagy via the LPA3/AKT/mTOR Pathway. *Frontiers in Physiology* **2018**, *9*, 1315, 10.3389/fphys.2018.01315.
35. Yan Liao; Ganggang Mu; Lingli Zhang; Wei Zhou; Jun Zhang; Honggang Yu; Lysophosphatidic Acid Stimulates Activation of Focal Adhesion Kinase and Paxillin and Promotes Cell Motility, via LPA1–3, in Human Pancreatic Cancer. *Digestive Diseases and Sciences* **2013**, *58*, 3524-3533, 10.1007/s10620-013-2878-4.
36. Junken Aoki; Two pathways for lysophosphatidic acid production. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* **2008**, *1781*, 513-518, 10.1016/j.bbalip.2008.06.005.
37. Helgi B. Schiöth; Robert Fredriksson; The GRAFS classification system of G-protein coupled receptors in comparative perspective. *General and Comparative Endocrinology* **2005**, *142*, 94-101, 10.1016/j.ygcen.2004.12.018.
38. Matthew N. Davies; Andrew Secker; Alex Freitas; Miguel Mendao; Jonathan Ian Timmis; Darren R. Flower; On the hierarchical classification of G protein-coupled receptors. *Bioinformatics* **2007**, *23*, 3113-3118, 10.1093/bioinformatics/btm506.
39. Yoh Takuwa; Noriko Takuwa; Naotoshi Sugimoto; The Edg Family G Protein-Coupled Receptors for Lysophospholipids: Their Signaling Properties and Biological Activities. *The Journal of Biochemistry* **2002**, *131*, 767-771, 10.1093/oxfordjournals.jbchem.a003163.
40. Kim A Neve , Jeremy K Seamans, Heather Trantham-Davidson; Dopamine receptor signaling. *J Recept Signal Transduct Res* **2004**, *24*, 165-205, 10.1081/rrs-200029981.
41. Mu-En Lin; Deron R. Herr; Jerold Chun; Lysophosphatidic acid (LPA) receptors: Signaling properties and disease relevance. *Prostaglandins & Other Lipid Mediators* **2010**, *91*, 130-138, 10.1016/j.prostaglandins.2009.02.002.
42. Stéphane Dalle; Takeshi Imamura; David W. Rose; Dorothy Sears Worrall; Satoshi Ugi; Christopher J. Hupfeld; Jerrold M. Olefsky; Insulin Induces Heterologous Desensitization of G Protein-Coupled Receptor and Insulin-Like Growth Factor I Signaling by Downregulating β-Arrestin-1. *Molecular and Cellular Biology* **2002**, *22*, 6272-6285, 10.1128/mcb.22.17.6272-6285.2002.
43. Davide Calebiro; Amod Godbole; Internalization of G-protein-coupled receptors: Implication in receptor function, physiology and diseases. *Best Practice & Research Clinical Endocrinology & Metabolism* **2018**, *32*, 83-91, 10.1016/j.beem.2018.01.004.
44. Qisheng Liu; Mark S. Bee; Agnes Schonbrunn; Site Specificity of Agonist and Second Messenger-Activated Kinases for Somatostatin Receptor Subtype 2A (Sst2A) Phosphorylation. *Molecular Pharmacology* **2009**, *76*, 68-80, 10.1124/mol.108.054262.
45. Richard Premont; James Inglese; Robert J. Lefkowitz; Protein kinases that phosphorylate activated G protein-coupled receptors. *The FASEB Journal* **1995**, *9*, 175-182, 10.1096/fasebj.9.2.7781920.
46. Marco A. Alfonzo-Méndez; Gabriel Carmona-Rosas; David A. Hernández-Espinosa; M. Teresa Romero-Ávila; J. Adolfo García-Sáinz; Different phosphorylation patterns regulate α1D-adrenoceptor signaling and desensitization. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* **2018**, *1865*, 842-854, 10.1016/j.bbamcr.2018.03.006.

47. Denise Wootten; Arthur Christopoulos; Maria Marti-Solano; M. Madan Babu; Patrick M. Sexton; Mechanisms of signalling and biased agonism in G protein-coupled receptors. *Nature Reviews Molecular Cell Biology* **2018**, *19*, 638-653, 10.1038/s41580-018-0049-3.

48. Stuart J. Mundell; Matthew L. Jones; Adam R. Hardy; Johanna F. Barton; Stephanie Beaucourt; Pamela B. Conley; Alastair W. Poole; Distinct Roles for Protein Kinase C Isoforms in Regulating Platelet Purinergic Receptor Function. *Molecular Pharmacology* **2006**, *70*, 1132-1142, 10.1124/mol.106.023549.

49. Mandi M. Murph; Launa A. Scaccia; Laura A. Volpicelli; Harish Radhakrishna; Agonist-induced endocytosis of lysophosphatidic acid-coupled LPA1/EDG-2 receptors via a dynamin2- and Rab5-dependent pathway. *Journal of Cell Science* **2003**, *116*, 1969-1980, 10.1242/jcs.00397.

50. Ana C Magalhaes; Henry A. Dunn; Stephen Sg Ferguson; Regulation of GPCR activity, trafficking and localization by GPCR-interacting proteins. *Journal of Cerebral Blood Flow & Metabolism* **2012**, *165*, 1717-1736, 10.1111/j.1476-5381.2011.01552.x.

51. Fangtian Huang; Anastasia Khvorova; William Marshall; Alexander Sorkin; Analysis of Clathrin-mediated Endocytosis of Epidermal Growth Factor Receptor by RNA Interference. *Journal of Biological Chemistry* **2004**, *279*, 16657-16661, 10.1074/jbc.c400046200.

52. Braden T. Lobingier; Mark Von Zastrow; When trafficking and signaling mix: How subcellular location shapes G protein-coupled receptor activation of heterotrimeric G proteins. *Traffic* **2018**, *20*, 130-136, 10.1111/tra.12634.

53. Stephan K. Böhm; Lev M. Khitin; Steven P. Smeekens; Eileen F. Grady; Donald G. Payan; Nigel W. Bunnett; Identification of Potential Tyrosine-containing Endocytic Motifs in the Carboxyl-tail and Seventh Transmembrane Domain of the Neurokinin 1 Receptor. *Journal of Biological Chemistry* **1996**, *272*, 2363-2372, 10.1074/jbc.272.4.2363.

54. Alexander Zaslavsky; Lisam Shanjukumar Singh; Haiyan Tan; Huawen Ding; Zicai Liang; Yan Xu; Homo- and hetero-dimerization of LPA/S1P receptors, OGR1 and GPR4. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* **2006**, *1761*, 1200-1212, 10.1016/j.bbalip.2006.08.011.

55. Koji Bandoh; Junken Aoki; Akitsu Taira; Masafumi Tsujimoto; Hiroyuki Arai; Keizo Inoue; Lysophosphatidic acid (LPA) receptors of the EDG family are differentially activated by LPA species. *FEBS Letters* **2000**, *478*, 159-165, 10.1016/s0014-5793(00)01827-5.

56. Koji Bandoh; Junken Aoki; Hiroyuki Hosono; Susumu Kobayashi; Tetsuyuki Kobayashi; Kimiko Murakami-Murofushi; Masafumi Tsujimoto; Hiroyuki Arai; Keizo Inoue; Molecular Cloning and Characterization of a Novel Human G-protein-coupled Receptor, EDG7, for Lysophosphatidic Acid. *Journal of Biological Chemistry* **1999**, *274*, 27776-27785, 10.1074/jbc.274.39.27776.

57. Rocío Alcántara-Hernández; Aurelio Hernández-Méndez; Gisselle A. Campos-Martínez; Aldo Meizoso Huesca; J. Adolfo García-Sáinz; Phosphorylation and Internalization of Lysophosphatidic Acid Receptors LPA1, LPA2, and LPA3. *PLOS ONE* **2015**, *10*, e0140583, 10.1371/journal.pone.0140583.

58. James I. Fells; Ryoko Tsukahara; Jianxiong Liu; Gabor Tigyi; Abby L. Parrill; Structure-based drug design identifies novel LPA3 antagonists. *Bioorganic & Medicinal Chemistry* **2009**, *17*, 7457-7464, 10.1016/j.bmc.2009.09.022.

59. Shimeng Guo; Jiandong Zhang; Shuyong Zhang; Jing Li; A Single Amino Acid Mutation (R104P) in the E/DRY Motif of GPR40 Impairs Receptor Function. *PLOS ONE* **2015**, *10*, e0141303, 10.1371/journal.pone.0141303.

60. Kate L. White; Matthew T. Eddy; Zhan-Guo Gao; Gye Won Han; Tiffany Lian; Alexander Deary; Nilkanth Patel; Kenneth Jacobson; Vsevolod Katritch; Raymond C. Stevens; et al. Structural Connection between Activation Microswitch and Allosteric Sodium Site in GPCR Signaling. *Structure* **2018**, *26*, 259-269.e5, 10.1016/j.str.2017.12.013.

61. Mireia Olivella; Gianluigi Caltabiano; Arnau Cordomí; The role of Cysteine 6.47 in class A GPCRs. *BMC Structural Biology* **2012**, *13*, 3-3, 10.1186/1472-6807-13-3.

62. You-Me Kim; Jeffrey L. Benovic; Differential Roles of Arrestin-2 Interaction with Clathrin and Adaptor Protein 2 in G Protein-coupled Receptor Trafficking. *Journal of Biological Chemistry* **2002**, *277*, 30760-30768, 10.1074/jbc.m204528200.

63. May M. Paing; Christopher A. Johnston; David P. Siderovski; Joann Trejo; Clathrin Adaptor AP2 Regulates Thrombin Receptor Constitutive Internalization and Endothelial Cell Resensitization. *Molecular and Cellular Biology* **2006**, *26*, 3231-42, 10.1128/mcb.26.8.3231-3242.2006.

64. Breann L. Wolfe; Joann Trejo; Clathrin-Dependent Mechanisms of G Protein-coupled Receptor Endocytosis. *Traffic* **2007**, *8*, 462-470, 10.1111/j.1600-0854.2007.00551.x.

65. Owen N. Vickery; Catarina A. Carvalheda; Saheem Zaidi; Andrei Pisliakov; Vsevolod Katritch; Ulrich Zachariae; Intracellular Transfer of Na+ in an Active-State G-Protein-Coupled Receptor. *Structure* **2017**, *26*, 171-180.e2, 10.1016/j.str.2017.11.013.

66. G. Enrico Rovati; Valérie Capra; Vincent S. Shaw; Rabia U. Malik; Sivaraj Sivaramakrishnan; Richard R. Neubig; The DRY motif and the four corners of the cubic ternary complex model. *Cellular Signalling* **2017**, *35*, 16-23, 10.1016/j.cellsig.2017.03.020.

67. Qingtong Zhou; Dehua Yang; Meng Wu; Yu Guo; Wangjing Guo; Li Zhong; Xiaoqing Cai; Antao Dai; Wonjo Jang; Eugene I Shakhnovich; et al. Common activation mechanism of class A GPCRs. *eLife* **2019**, *8*, e50279, 10.7554/elife.50279.

68. Shuguang Yuan; Activation Of G-Protein-Coupled Receptors Correlates With The Formation Of A Continuous Internal Water Pathway. *null* **2015**, *5*, 4733, 10.5281/zenodo.32732.

69. Xuejun C. Zhang; Ye Zhou; Can Cao; Proton transfer during class-A GPCR activation: do the CWxP motif and the membrane potential act in concert?. *Biophysics Reports* **2018**, *4*, 115-122, 10.1007/s41048-018-0056-0.

70. Irina S. Moreira; Structural features of the G-protein/GPCR interactions. *Biochimica et Biophysica Acta (BBA) - General Subjects* **2013**, *1840*, 16-33, 10.1016/j.bbagen.2013.08.027.

71. Daniel Wacker; Raymond Stevens; Bryan L. Roth; How Ligands Illuminate GPCR Molecular Pharmacology. *Cell* **2017**, *170*, 414-427, 10.1016/j.cell.2017.07.009.

72. Ieva Sutkeviciute; Jean-Pierre Vilardaga; Structural insights into emergent signaling modes of G protein–coupled receptors. *Journal of Biological Chemistry* **2020**, *295*, 11626-11642, 10.1074/jbc.rev120.009348.

73. Iban Ubarretxena-Belandia; Donald M Engelman; Helical membrane proteins: diversity of functions in the context of simple architecture. *Current Opinion in Structural Biology* **2001**, *11*, 370-376, 10.1016/s0959-440x(00)00217-7.

74. A E Alewijnse; H Timmerman; E H Jacobs; M J Smit; E Roovers; S Cotecchia; R Leurs; The effect of mutations in the DRY motif on the constitutive activity and structural instability of the histamine H(2) receptor.. *Molecular Pharmacology* **2000**, *57*, 890–898, .

75. Rong He; Darren D. Browning; Richard D. Ye; Differential roles of the NPXXY motif in formyl peptide receptor signaling.. *The Journal of Immunology* **2001**, *166*, 4099-4105, 10.4049/jimmunol.166.6.4099.

76. Duane A Chung; Susan M Wade; Carol B Fowler; Danielle D Woods; Paolo B Abada; Henry I Mosberg; Richard R Neubig; Mutagenesis and peptide analysis of the DRY motif in the α2A adrenergic receptor: evidence for alternate mechanisms in G protein-coupled receptors. *Biochemical and Biophysical Research Communications* **2002**, *293*, 1233-1241, 10.1016/s0006-291x(02)00357-1.

77. X. Edward Zhou; Yuanzheng He; Parker de Waal; Xiang Gao; Yanyong Kang; Ned Van Eps; Yanting Yin; Kuntal Pal; Devrishi Goswami; Thomas A. White; et al. Identification of Phosphorylation Codes for Arrestin Recruitment by G Protein-Coupled Receptors. *Cell* **2017**, *170*, 457-469.e13, 10.1016/j.cell.2017.07.002.

78. Daniel Mayer; Fred F. Damberger; Mamidi Samarasimhareddy; Miki Feldmueller; Ziva Vuckovic; Tilman Flock; Brian Bauer; Eshita Mutt; Franziska Zosel; Frédéric H. T. Allain; et al. Distinct G protein-coupled receptor phosphorylation motifs modulate arrestin affinity and activation and global conformation. *Nature Communications* **2019**, *10*, 1261, 10.1038/s41467-019-09204-y.

79. Yuko Fujiwara; Vineet Sardar; Akira Tokumura; Daniel Baker; Kimiko Murakami-Murofushi; Abby Parrill; Gabor Tigyi; Identification of Residues Responsible for Ligand Recognition and Regioisomeric Selectivity of Lysophosphatidic Acid Receptors Expressed in Mammalian Cells. *Journal of Biological Chemistry* **2005**, *280*, 35038-35050, 10.1074/jbc.m504351200.

80. William J. Valentine; James I. Fells; Donna H. Perygin; Sana Mujahid; Kazuaki Yokoyama; Yuko Fujiwara; Ryoko Tsukahara; James R. Van Brocklyn; Abby L. Parrill; Gabor Tigyi; et al. Subtype-specific Residues Involved in Ligand Activation of the Endothelial Differentiation Gene Family Lysophosphatidic Acid Receptors. *Journal of Biological Chemistry* **2008**, *283*, 12175-12187, 10.1074/jbc.m708847200.

81. Robert G. Kaye; José W. Saldanha; Zhi-Liang Lu; Edward C. Hulme; Helix 8 of the M1 Muscarinic Acetylcholine Receptor: Scanning Mutagenesis Delineates a G Protein Recognition Site. *Molecular Pharmacology* **2011**, *79*, 701-709, 10.1124/mol.110.070177.

82. Noel M. Delos Santos; Lidia A. Gardner; Stephen W. White; Suleiman W. Bahouth; Characterization of the Residues in Helix 8 of the Human β1-Adrenergic Receptor That Are Involved in Coupling the Receptor to G Proteins. *Journal of Biological Chemistry* **2006**, *281*, 12896-12907, 10.1074/jbc.m508500200.

83. John Huynh; Walter Glen Thomas; Marie-Isabel Aguilar; Leonard Keith Pattenden; Role of helix 8 in G protein-coupled receptors based on structure–function studies on the type 1 angiotensin receptor. *Molecular and Cellular Endocrinology* **2009**, *302*, 118-127, 10.1016/j.mce.2009.01.002.

84. Patricia M. Dijkman; Juan C. Muñoz-García; Steven R. Lavington; Patricia Suemy Kumagai; Rosana Inacio dos Reis; Daniel Yin; Phillip J. Stansfeld; Antonio José Costa-Filho; Anthony Watts; Conformational dynamics of a G protein–

coupled receptor helix 8 in lipid membranes. *Science Advances* **2020**, *6*, eaav8207, 10.1126/sciadv.aav8207.

85. Catalina Ribas; Petronila Penela; Cristina Murga; Alicia Salcedo; Carlota García-Hoz; María Jurado-Pueyo; Ivette Aymerich; Federico Mayor; The G protein-coupled receptor kinase (GRK) interactome: Role of GRKs in GPCR regulation and signaling. *Biochimica et Biophysica Acta (BBA) - Biomembranes* **2007**, *1768*, 913-922, 10.1016/j.bbamem.2006.09.019.
86. Vsevolod V. Gurevich; Xiufeng Song; Sergey A. Vishnivetskiy; Eugenia V. Gurevich; Enhanced Phosphorylation-Independent Arrestins and Gene Therapy. *Organotypic Models in Drug Development* **2013**, *219*, 133-152, 10.1007/978-3-642-41199-1_7.
87. Alexey N. Pronin; Christopher V. Carman; Jeffrey L. Benovic; Structure-Function Analysis of G Protein-coupled Receptor Kinase-5. *Journal of Biological Chemistry* **1998**, *273*, 31510-31518, 10.1074/jbc.273.47.31510.
88. Kenji Watari; Michio Nakaya; Hitoshi Kurose; Multiple functions of G protein-coupled receptor kinases. *Journal of Molecular Signaling* **2014**, *9*, 1-1, 10.1186/1750-2187-9-1.
89. Matthew T. Drake; Sudha K. Shenoy; Robert J. Lefkowitz; Trafficking of G Protein–Coupled Receptors. *Circulation Research* **2006**, *99*, 570-582, 10.1161/01.res.0000242563.47507.ce.
90. Eric Reiter; Robert J. Lefkowitz; GRKs and β-arrestins: roles in receptor silencing, trafficking and signaling. *Trends in Endocrinology & Metabolism* **2006**, *17*, 159-165, 10.1016/j.tem.2006.03.008.
91. Mithu Baidya; Punita Kumari; Hemlata Dwivedi-Agnihotri; Shubhi Pandey; Madhu Chaturvedi; Tomasz Maciej Stepniewski; Kouki Kawakami; Yubo Cao; Stéphane A Laporte; Jana Selent; et al. Key phosphorylation sites in GPCRs orchestrate the contribution of β-Arrestin 1 in ERK 1/2 activation. *EMBO reports* **2020**, *21*, e49886, 10.15252/embr.201949886.
92. Ozge Sensoy; Irina Sousa Moreira; Giulia Morra; Understanding the Differential Selectivity of Arrestins toward the Phosphorylation State of the Receptor. *ACS Chemical Neuroscience* **2016**, *7*, 1212-1224, 10.1021/acschemneuro.6b00073.
93. Roxanne A. Ally; Kirk L. Ives; Elie Traube; Iman Eltounsi; Pei-Wen Chen; Patrick J. Cahill; James F. Battey; Mark R. Hellmich; Glenn S. Kroog; Agonist- and Protein Kinase C-Induced Phosphorylation Have Similar Functional Consequences for Gastrin-Releasing Peptide Receptor Signaling via Gq. *Molecular Pharmacology* **2003**, *64*, 890-904, 10.1124/mol.64.4.890.
94. JiHee Kim; SeungKirl Ahn; Xiu-Rong Ren; Erin J. Whalen; Eric Reiter; Huijun Wei; Robert J. Lefkowitz; Functional antagonism of different G protein-coupled receptor kinases for -arrestin-mediated angiotensin II receptor signaling. *Proceedings of the National Academy of Sciences* **2005**, *102*, 1442-1447, 10.1073/pnas.0409532102.
95. Tilman Flock; Charles N. J. Ravarani; Dawei Sun; A. J. Venkatakrishnan; Melis Kayikci; Christopher G. Tate; Dmitry Veprintsev; M. Madan Babu; Universal allosteric mechanism for Gα activation by GPCRs. *Nature* **2015**, *524*, 173-179, 10.1038/nature14663.
96. Adrian J. Butcher; Rudi Prihandoko; Kok Choi Kong; Phillip McWilliams; Jennifer M. Edwards; Andrew Bottrill; Sharad Mistry; Andrew B. Tobin; Differential G-protein-coupled Receptor Phosphorylation Provides Evidence for a Signaling Bar Code. *Journal of Biological Chemistry* **2011**, *286*, 11506-11518, 10.1074/jbc.m110.154526.
97. Aurelio Hernández-Méndez; Rocío Alcántara-Hernández; J. Adolfo García-Sáinz; Lysophosphatidic acid LPA1-3 receptors: signaling, regulation and in silico analysis of their putative phosphorylation sites. *Receptors & Clinical Investigation* **2014**, *1*, 10, 10.14800/rci.193.
98. Shan Yu; Litao Sun; Yufei Jiao; Leo Tsz On Lee; The Role of G Protein-coupled Receptor Kinases in Cancer. *International Journal of Biological Sciences* **2017**, *14*, 189-203, 10.7150/ijbs.22896.
99. Joseph B. Black; Richard T. Premont; Yehia Daaka; Feedback regulation of G protein-coupled receptor signaling by GRKs and arrestins. *Seminars in Cell & Developmental Biology* **2016**, *50*, 95-104, 10.1016/j.semcdb.2015.12.015.
100. David T. Lodowski; Julie A. Pitcher; W. Darrell Capel; Robert J. Lefkowitz; John J. G. Tesmer; Keeping G Proteins at Bay: A Complex Between G Protein-Coupled Receptor Kinase 2 and Gbetagamma. *Science* **2003**, *300*, 1256-1262, 10.1126/science.1082348.
101. Elisabeth Cassier; Nathalie Gallay; Thomas Bourquard; Sylvie Claeysen; Joël Bockaert; Pascale Crépieux; Anne Poupon; Eric Reiter; Philippe Marin; Franck Vandermoere; et al. Phosphorylation of β-arrestin2 at Thr383 by MEK underlies β-arrestin-dependent activation of Erk1/2 by GPCRs. *eLife* **2017**, *6*, e23777, 10.7554/elife.23777.
102. Huijun Wei; SeungKirl Ahn; Sudha K. Shenoy; Sadashiva S. Karnik; László Hunyady; Louis M. Luttrell; Robert J. Lefkowitz; Independent -arrestin 2 and G protein-mediated pathways for angiotensin II activation of extracellular signal-regulated kinases 1 and 2. *Proceedings of the National Academy of Sciences* **2003**, *100*, 10782-10787, 10.1073/pnas.1834556100.

103. Cristina Murga; Ana Ruiz-Gómez; Irene García-Higuera; Chong M. Kim; Jeffrey L. Benovic; Federico Mayor; High Affinity Binding of β-Adrenergic Receptor Kinase to Microsomal Membranes: MODULATION OF THE ACTIVITY OF BOUND KINASE BY HETEROTRIMERIC G PROTEIN ACTIVATION. *Journal of Biological Chemistry* **1996**, *271*, 985-994, 10.1074/jbc.271.2.985.

104. Takako Shiina; Ken Arai; Shihori Tanabe; Norihiro Yoshida; Tatsuya Haga; Taku Nagao; Hitoshi Kurose; Clathrin Box in G Protein-coupled Receptor Kinase 2. *Journal of Biological Chemistry* **2001**, *276*, 33019-33026, 10.1074/jbc.m100140200.

105. Sandra Peregrin; Maria Jurado-Pueyo; Pedro M. Campos; Victoria Sanz-Moreno; Ana Ruiz-Gomez; Piero Crespo; Federico Mayor; Cristina Murga; Phosphorylation of p38 by GRK2 at the Docking Groove Unveils a Novel Mechanism for Inactivating p38MAPK. *Current Biology* **2006**, *16*, 2042-2047, 10.1016/j.cub.2006.08.083.

106. Christopher V. Carman; Larry S. Barak; Chongguang Chen; Lee-Yuan Liu-Chen; James J. Onorato; Scott P. Kennedy; Marc G. Caron; Jeffrey L. Benovic; Mutational Analysis of Gβγ and Phospholipid Interaction with G Protein-coupled Receptor Kinase 2. *Journal of Biological Chemistry* **2000**, *275*, 10443-10452, 10.1074/jbc.275.14.10443.

107. Suleiman W. Bahouth; Mohammed M. Nooh; Barcoding of GPCR trafficking and signaling through the various trafficking roadmaps by compartmentalized signaling networks. *Cellular Signalling* **2017**, *36*, 42-55, 10.1016/j.cellsig.2017.04.015.

108. Zhao Yang; Fan Yang; Daolai Zhang; Zhixin Liu; Amy Lin; Chuan Liu; Peng Xiao; Xiao Yu; Jin-Peng Sun; Phosphorylation of G Protein-Coupled Receptors: From the Barcode Hypothesis to the Flute Model. *Molecular Pharmacology* **2017**, *92*, 201-210, 10.1124/mol.116.107839.
