G Protein-Coupled Receptors

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GPCRs arguably represent the most effective current therapeutic targets for a plethora of diseases. GPCRs also possess a pivotal role in the regulation of the physiological balance between healthy and pathological conditions; thus, their importance in systems biology cannot be underestimated. The molecular diversity of GPCR signaling systems is likely to be closely associated with disease-associated changes in organismal tissue complexity and compartmentalization, thus enabling a nuanced GPCR-based capacity to interdict multiple disease pathomechanisms at a systemic level. GPCRs have been long considered as controllers of communication between tissues and cells. This communication involves the ligand-mediated control of cell surface receptors that then direct their stimuli to impact cell physiology.

G protein-coupled receptor network pharmacology

1. G Protein-Coupled Receptors

It is reasonable to contend that the most therapeutically important molecular targets at the present time are the transmembrane heptahelical G protein-coupled receptors (GPCR). GPCRs are the largest family of transmembrane receptors in humans and many other species and represent the most diverse family of targets for current therapeutics [1][2][3][4]. GPCRs facilitate communication between cells in tissues across long distances in the body, thereby enabling the capacity for system-level therapy [5][6][7][8]. Therapeutics effectively exploited GPCR systems many years even before the discovery of GPCRs themselves [9][10]. Controllers of these receptors were originally designed to exert either a simple positive effect (increasing the activity of downstream signaling systems, e.g., adenylate cyclase) or by inhibiting this activity by occupying the receptor and antagonizing the positive actions of stimulatory ligands. Therapeutic agents were classified as simple agonists or antagonists based on the concept that receptors could exist predominantly in two distinct states, i.e., inactive and active.

Work from multiple talented laboratories nearly three decades later largely confirmed this two-state model for GPCRs [11][12][13][14][15][16][17]. With the introduction of molecular alterations to GPCRs [18], it was demonstrated that GPCRs indeed exist in a spontaneous equilibrium between two conformations, i.e., active (R*) and inactive (R). The active conformation is stabilized by agonist binding or by mutagenesis that can relieve intramolecular constraints [18][19][20][21][22][23]. In this model, GPCRs transmit signals through their capacity to act as guanine nucleotide exchange factors for the heterotrimeric guanine nucleotide-binding proteins (G proteins) in response to stimulatory ligand binding. G protein activation is initiated through conformational rearrangement of the GPCR transmembrane core and juxtamembrane loop regions, eventually catalyzing the exchange of GDP for GTP on the receptor-associated Gα subunit [24][25][26][27][28]. A guanine nucleotide exchange (GDP for GTP) then initiates the dissociation of the heterotrimeric G protein from the GPCR, followed by the break-up of the G protein heterotrimer releasing free GTP-bound α and βγ subcomplexes. These two signaling components can stimulate, inhibit or physically recruit multiple downstream signal transduction effectors, e.g., adenylyl cyclase (AC), phospholipase C (PLC), GPCR kinases (GRKs) or GRK-interacting proteins [29]. In this manner, the heterotrimeric G protein can transmit information to the intracellular milieu about the qualitative and quantitative nature of a specific extracellular stimuli [30][31].

2. Signaling Diversity in GPCRs

2.1. G Protein and Non-G Protein Signaling

Since their discovery, GPCRs have been considered to be primarily G protein-signaling entities. This knowledge has been demonstrated to be exceptionally successful in allowing the creation of a huge variety of effective pharmacotherapeutics. Hauser et al. evaluated in 2017 that 475 FDA-approved drugs target GPCRs, which is 34% of all FDA-approved drugs [32]. Even with this specific G protein focus, agents have been generated that can control the bias amongst diverse forms of G protein-signaling output [23][33]. In the last decade, our appreciation of GPCR-signaling complexity has been enhanced by the demonstration of simultaneous signaling activities emanating from GPCRs that are either G protein-based or controlled by non-G protein-signaling adaptors. Even with just the primary consideration of G protein activation, it is evident that the receptor conformations for G protein activation are different between specific G protein pools and that synthetic and naturally occurring ligands can selectively facilitate the formation of different receptor coupling conformations [23][34]. Multiple distinct forms of agonist ligands for a single GPCR type have now been discovered to only activate a subset of G proteins or a subset of downstream signaling effectors or induce G protein coupling without initiating internalization and desensitization [23][35][36]. Given the successful exploitation of the therapeutic intervention of GPCR-based G protein signaling, it is likely that it will be possible to improve this index even further by exploiting the true complexity and diversity of GPCR signaling [32][37]. Apart from the classical G protein signaling, multiple research lines have pointed towards the presence of non-G protein-based signaling, mainly through β-arrestins [38][39][40]. One of the first studied examples of this novel signaling activity was the β-arrestin-dependent activation of extracellular signal-regulated kinases 1/2 (ERK 1/2) [29][41]. Compared to the rapid and transient manner of G protein signaling [39], β-arrestin-linked pathway activation has a later onset but is sustained over a long period and entrains long-term l cellular transcriptional and proteomic effects [42][43][44][45]. β-arrestin also serves as a negative regulatory protein for signaling through G proteins and is responsible for GPCR internalization [45][46][47]. However, there is still some dispute in the field with respect to the interdependence of G protein and β-arrestin signaling; recently, complete G protein independence could not be proven in a serum-starved in vitro G protein knockout model [41]. Evidence has also been revealed recently that suggests that certain specific forms of orphan receptors (D6R and C5aR2) appear to be able to functionally interact with β-arrestins but not with G proteins [48]. This data reinforces the posit that there are likely a diverse range of receptorsome entities that are prewired to specific independent downstream signaling pathways.

2.2. G Protein-Coupled Receptor Complexes

Since 1999, it has become clear that GPCR signaling is more complex, specific and diverse than initially considered in the two-state model [28][49]. One of the factors accounting for this complexity is the ability of receptors to form multistate-signaling complexes or so-called receptorsome structures. These receptorsome structures comprise the receptor itself combined with multiple interacting proteins. These preassembled receptorsomes demonstrate unique pharmacology, signaling, trafficking, desensitization and internalization features [50][51][52][53]. This conditioning of GPCR activity is also influenced by the relative variations of these adaptor proteins in distinct tissues, suggesting the presence of tissue-specific GPCR activity [23][37][54]. Given this growth in GPCR-signaling complexity, it is vital to recognize the unique properties of endogenous or cognate ligands for GPCRs. The proposed cognate ligands of GPCRs attempt to impact every consequence of receptor activation in the same manner, whether desensitization, internalization, trafficking or G protein coupling [43][55]. Hence, these ligands strive to engender an omnipotent efficacy. The ability of a ligand to achieve this at a systemic multi-tissue level is, however, highly unlikely due to tissue-to-tissue variations in the receptor and signaling adaptor expression under the influence of diverse cellular conditions [23][56][57][58][59]. Given the ability for multiple ligands to stimulate the same GPCR, it may be prudent to redefine our conceptualization of endogenous ligand cognation. Indeed, the most accurate definition of a cognate ligand for a specific GPCR could be codified by its ability to most equally regulate the full GPCR-signaling spectrum across a diverse series of tissue/cell settings. Hence, it is likely that receptors and their cognate ligands coevolved to elicit the most physiologically adaptive and effective responses in target cells. With respect to the concept of functional relationships between cognate ligands and their preferred receptors, the aging/stress response paradigm presents an important pathophysiological process that represents perhaps the greatest systemic and coordinated perturbation of cellular signaling in human physiology.

This complexity and diversity of GPCR signaling also reveals the necessity to change our definition of agonists and antagonists originally based on the two-state model [18][19][20][21][22]. Ligands, to varying degrees, likely stabilize these different active conformational states and thereby initiate diverse signaling pathways. This concept is known as biased agonism. Verifying and understanding this mechanism will likely help to develop functionally selective drugs, which activate beneficial downstream pathways and suppress adverse side effects [23][24].

It is evident that an in-depth understanding of the effective G protein-coupling capacity of GPCRs has been effective for the development of GPCR-based therapeutics [60]. The G protein-centric focus of GPCR signaling was expanded by the discovery that β-arrestins—originally thought of just as terminators of G protein signaling [61][62]—can also act as productive signaling effectors [49]. Further research has demonstrated that the realm of GPCR signaling is far more complex and diverse than initially imagined [2][37][43]. This signaling diversity arises from several factors associated with subcellular localization, specific post-translational modification states of the receptor and, perhaps most importantly, the ability of the receptor to exist in multiple receptorsome-signaling states. In multistate signaling GPCR models, specific agonists likely possess the ability to activate distinct active receptorsomes by exposing different intracellular regions involved in coupling separate G protein pools, initially demonstrated for the β2-adrenergic receptor antagonist ICI-118-551 [63][64], and β-arrestin signaling [45][49]. It is becoming more evident each year that agonist-selective receptor signaling, targeting a subset of the possible response profiles, may represent an opportunity to develop drugs that are more precise and could also have an increased efficacy.

To assist the capacity to investigate these GPCR receptorsomes, there have been considerable advances in the accuracy and selectivity of proteomics-focused mass spectrometers that can investigate the specific protein stoichiometries in these complexes. This increase of protein detection sensitivity has enabled the experimental transition from whole-tissue/cell investigation to allow an analysis of protein–protein interactions at a subcellular level, i.e., interactomics [65]. The dynamic investigation of how multiprotein complexes alter in quantity and quality in response to drug exposure has enabled the examination of the subcellular network functionality of therapeutic agents [66][67][68][69]. The importance of GPCR interactomics lies in the posit that the local context of protein associations/interactions is often more strongly linked to the biological activity of a certain form of signaling pathway or disease process, as opposed to simple global cellular or tissue protein expression levels [68][70].

2.3. G Protein Signaling, Endocytosis and Cellular Location

The canonical model of GPCR signaling, either through G proteins or non-G protein adaptors, has been largely considered to emanate from the plasma membrane localized receptors. One potential mechanism contributing to the diversity and specificity of GPCR signaling is through membrane trafficking and alternative residential and signaling sites of the receptor [71][72][73]. Until recently, the cell surface plasma membrane trafficking of GPCRs was considered as a mechanism to control the sensitivity to an extracellular stimulus by changing the receptor level through ligand-mediated endocytosis or reduced trafficking to the plasma membrane of newly synthesized receptors [74]. It has recently been demonstrated that GPCRs can signal from intracellular membranes such as endosomes, mitochondria, the endoplasmic reticulum, the Golgi apparatus and the nucleus [75][76]. This shift in signaling location was first identified on Gαs-coupled receptors such as the parathyroid receptor, thyroid-stimulating hormone receptor and the β2 adrenergic receptor, where cyclic adenosine monophosphate production was still evident after endocytosis [77]. Given the subcellular variations of GPCR adaptor protein expression, it is highly likely that the subcellular location of GPCR receptorsomes can assist in defining specific ensembles of adaptor-directed specific signaling activity [43].

References

1. Sriram, K.; Insel, P.A. G Protein-Coupled Receptors as Targets for Approved Drugs: How Many Targets and How Many Drugs? Mol. Pharmacol. 2018, 93, 251–258.
2. van Gastel, J.; Leysen, H.; Boddaert, J.; Vangenechten, L.; Luttrell, L.M.; Martin, B.; Maudsley, S. Aging-related modifications to G protein-coupled receptor signaling diversity. Pharmacol. Ther. 2021, 223, 107793.
3. Rask-Andersen, M.; Masuram, S.; Schiöth, H.B. The druggable genome: Evaluation of drug targets in clinical trials suggests major shifts in molecular class and indication. Annu. Rev. Pharmacol. Toxicol. 2014, 54, 9–26.
4. Santos, R.; Ursu, O.; Gaulton, A.; Bento, A.P.; Donadi, R.S.; Bologa, C.G.; Karlsson, A.; Al-Lazikani, B.; Hersey, A.; Oprea, T.I.; et al. A comprehensive map of molecular drug targets. Nat.

Rev. Drug Discov. 2017, 16, 19–34.

5. Janssens, J.; Etienne, H.; Idriss, S.; Azmi, A.; Martin, B.; Maudsley, S. Systems-Level G Protein-Coupled Receptor Therapy Across a Neurodegenerative Continuum by the GLP-1 Receptor System. Front. Endocrinol. 2014, 5, 142.
6. Tse, L.H.; Wong, Y.H. GPCRs in Autocrine and Paracrine Regulations. Front. Endocrinol. 2019, 10, 428.
7. de Oliveira, P.G.; Ramos, M.L.S.; Amaro, A.J.; Dias, R.A.; Vieira, S.I. G(i/o)-Protein Coupled Receptors in the Aging Brain. Front. Aging Neurosci. 2019, 11, 89.
8. Husted, A.S.; Trauelsen, M.; Rudenko, O.; Hjorth, S.A.; Schwartz, T.W. GPCR-Mediated Signaling of Metabolites. Cell Metab. 2017, 25, 777–796.
9. Del Castillo, J.; Katz, B. Interaction at end-plate receptors between different choline derivatives. Proc. R. Soc. London. Ser. B Biol. Sci. 1957, 146, 369–381.
10. Stephenson, R.P. A modification of receptor theory. Br. J. Pharmacol. Chemother. 1956, 11, 379–393.
11. De Lean, A.; Stadel, J.M.; Lefkowitz, R.J. A ternary complex model explains the agonist-specific binding properties of the adenylate cyclase-coupled beta-adrenergic receptor. J. Biol. Chem. 1980, 255, 7108–7117.
12. Gardella, T.J.; Luck, M.D.; Jensen, G.S.; Schipani, E.; Potts, J.T., Jr.; Jüppner, H. Inverse agonism of amino-terminally truncated parathyroid hormone (PTH) and PTH-related peptide (PTHrP) analogs revealed with constitutively active mutant PTH/PTHrP receptors. Endocrinology 1996, 137, 3936–3941.
13. Gether, U.; Lin, S.; Kobilka, B.K. Fluorescent labeling of purified beta 2 adrenergic receptor. Evidence for ligand-specific conformational changes. J. Biol. Chem. 1995, 270, 28268–28275.
14. Leff, P. The two-state model of receptor activation. Trends Pharmacol. Sci. 1995, 16, 89–97.
15. Parma, J.; Duprez, L.; Van Sande, J.; Cochaux, P.; Gervy, C.; Mockel, J.; Dumont, J.; Vassart, G. Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas. Nature 1993, 365, 649–651.
16. Pozvek, G.; Hilton, J.M.; Quiza, M.; Houssami, S.; Sexton, P.M. Structure/function relationships of calcitonin analogues as agonists, antagonists, or inverse agonists in a constitutively activated receptor cell system. Mol. Pharmacol. 1997, 51, 658–665.
17. Shenker, A.; Laue, L.; Kosugi, S.; Merendino, J.J., Jr.; Minegishi, T.; Cutler, G.B., Jr. A constitutively activating mutation of the luteinizing hormone receptor in familial male precocious puberty. Nature 1993, 365, 652–654.

18. Samama, P.; Cotecchia, S.; Costa, T.; Lefkowitz, R.J. A mutation-induced activated state of the beta 2-adrenergic receptor. Extending the ternary complex model. J. Biol. Chem. 1993, 268, 4625–4636.
19. Ceresa, B.P.; Limbird, L.E. Mutation of an aspartate residue highly conserved among G-protein-coupled receptors results in nonreciprocal disruption of alpha 2-adrenergic receptor-G-protein interactions. A negative charge at amino acid residue 79 forecasts alpha 2A-adrenergic receptor sensitivity to allosteric modulation by monovalent cations and fully effective receptor/G-protein coupling. J. Biol. Chem. 1994, 269, 29557–29564.
20. Morin, D.; Cotte, N.; Balestre, M.N.; Mouillac, B.; Manning, M.; Breton, C.; Barberis, C. The D136A mutation of the V2 vasopressin receptor induces a constitutive activity which permits discrimination between antagonists with partial agonist and inverse agonist activities. FEBS Lett. 1998, 441, 470–475.
21. Alewijnse, A.E.; Timmerman, H.; Jacobs, E.H.; Smit, M.J.; Roovers, E.; Cotecchia, S.; Leurs, R. The effect of mutations in the DRY motif on the constitutive activity and structural instability of the histamine H(2) receptor. Mol. Pharmacol. 2000, 57, 890–898.
22. Pauwels, P.J.; Tardif, S.; Wurch, T.; Colpaert, F.C. Facilitation of constitutive alpha(2A)-adrenoceptor activity by both single amino acid mutation (Thr(373)Lys) and g(alphao) protein coexpression: Evidence for inverse agonism. J. Pharmacol. Exp. Ther. 2000, 292, 654–663.
23. Maudsley, S.; Davidson, L.; Pawson, A.J.; Chan, R.; de Maturana, R.L.; Millar, R.P. Gonadotropin-releasing hormone (GnRH) antagonists promote proapoptotic signaling in peripheral reproductive tumor cells by activating a Galphai-coupling state of the type I GnRH receptor. Cancer Res. 2004, 64, 7533–7544.
24. Conklin, B.R.; Bourne, H.R. Structural elements of G alpha subunits that interact with G beta gamma, receptors, and effectors. Cell 1993, 73, 631–641.
25. Ernst, O.P.; Hofmann, K.P.; Sakmar, T.P. Characterization of rhodopsin mutants that bind transducin but fail to induce GTP nucleotide uptake. Classification of mutant pigments by fluorescence, nucleotide release, and flash-induced light-scattering assays. J. Biol. Chem. 1995, 270, 10580–10586.
26. Farahbakhsh, Z.T.; Hideg, K.; Hubbell, W.L. Photoactivated conformational changes in rhodopsin: A time-resolved spin label study. Science 1993, 262, 1416–1419.
27. Franke, R.R.; Sakmar, T.P.; Graham, R.M.; Khorana, H.G. Structure and function in rhodopsin. Studies of the interaction between the rhodopsin cytoplasmic domain and transducin. J. Biol. Chem. 1992, 267, 14767–14774.
28. Donnelly, D.; Maudsley, S.; Gent, J.P.; Moser, R.N.; Hurrell, C.R.; Findlay, J.B. Conserved polar residues in the transmembrane domain of the human tachykinin NK2 receptor: Functional roles

and structural implications. Biochem. J. 1999, 339 Pt 1, 55–61.

29. van Gastel, J.; Hendrickx, J.O.; Leysen, H.; Santos-Otte, P.; Luttrell, L.M.; Martin, B.; Maudsley, S. β-Arrestin Based Receptor Signaling Paradigms: Potential Therapeutic Targets for Complex Age-Related Disorders. Front. Pharmacol. 2018, 9, 1369.
30. Wess, J. G-protein-coupled receptors: Molecular mechanisms involved in receptor activation and selectivity of G-protein recognition. FASEB J. 1997, 11, 346–354.
31. Hamm, H.E. The many faces of G protein signaling. J. Biol. Chem. 1998, 273, 669–672.
32. Hauser, A.S.; Attwood, M.M.; Rask-Andersen, M.; Schiöth, H.B.; Gloriam, D.E. Trends in GPCR drug discovery: New agents, targets and indications. Nat. Rev. Drug Discov. 2017, 16, 829–842.
33. Gesty-Palmer, D.; Chen, M.; Reiter, E.; Ahn, S.; Nelson, C.D.; Wang, S.; Eckhardt, A.E.; Cowan, C.L.; Spurney, R.F.; Luttrell, L.M.; et al. Distinct beta-arrestin- and G protein-dependent pathways for parathyroid hormone receptor-stimulated ERK1/2 activation. J. Biol. Chem. 2006, 281, 10856–10864.
34. Kenakin, T. Biased Receptor Signaling in Drug Discovery. Pharmacol. Rev. 2019, 71, 267–315.
35. Kohout, T.A.; Nicholas, S.L.; Perry, S.J.; Reinhart, G.; Junger, S.; Struthers, R.S. Differential desensitization, receptor phosphorylation, beta-arrestin recruitment, and ERK1/2 activation by the two endogenous ligands for the CC chemokine receptor 7. J. Biol. Chem. 2004, 279, 23214–23222.
36. Sagan, S.; Chassaing, G.; Pradier, L.; Lavielle, S. Tachykinin peptides affect differently the second messenger pathways after binding to CHO-expressed human NK-1 receptors. J. Pharmacol. Exp. Ther. 1996, 276, 1039–1048.
37. Maudsley, S.; Leysen, H.; van Gastel, J.; Martin, B. Systems Pharmacology: Enabling Multidimensional Therapeutics; Elsevier: Amsterdam, The Netherlands, 2021.
38. Ferguson, S.S. Evolving concepts in G protein-coupled receptor endocytosis: The role in receptor desensitization and signaling. Pharmacol. Rev. 2001, 53, 1–24.
39. Coffa, S.; Breitman, M.; Spiller, B.W.; Gurevich, V.V. A single mutation in arrestin-2 prevents ERK1/2 activation by reducing c-Raf1 binding. Biochemistry 2011, 50, 6951–6958.
40. Gurevich, V.V.; Gurevich, E.V. Arrestins and G proteins in cellular signaling: The coin has two sides. Sci. Signal. 2018, 11, 549.
41. Grundmann, M.; Merten, N.; Malfacini, D.; Inoue, A.; Preis, P.; Simon, K.; Rüttiger, N.; Ziegler, N.; Benkel, T.; Schmitt, N.K.; et al. Lack of beta-arrestin signaling in the absence of active G proteins. Nat. Commun. 2018, 9, 341.

42. Luttrell, L.M.; Lefkowitz, R.J. The role of beta-arrestins in the termination and transduction of G-protein-coupled receptor signals. J. Cell Sci. 2002, 115, 455–465.
43. Maudsley, S.; Martin, B.; Luttrell, L.M. The origins of diversity and specificity in g protein-coupled receptor signaling. J. Pharmacol. Exp. Ther. 2005, 314, 485–494.
44. Maudsley, S.; Martin, B.; Gesty-Palmer, D.; Cheung, H.; Johnson, C.; Patel, S.; Becker, K.G.; Wood, W.H., 3rd; Zhang, Y.; Lehrmann, E.; et al. Delineation of a conserved arrestin-biased signaling repertoire in vivo. Mol. Pharmacol. 2015, 87, 706–717.
45. Gesty-Palmer, D.; Yuan, L.; Martin, B.; Wood, W.H., 3rd; Lee, M.H.; Janech, M.G.; Tsoi, L.C.; Zheng, W.J.; Luttrell, L.M.; Maudsley, S. β-arrestin-selective G protein-coupled receptor agonists engender unique biological efficacy in vivo. Mol. Endocrinol. 2013, 27, 296–314.
46. Pierce, K.L.; Maudsley, S.; Daaka, Y.; Luttrell, L.M.; Lefkowitz, R.J. Role of endocytosis in the activation of the extracellular signal-regulated kinase cascade by sequestering and nonsequestering G protein-coupled receptors. Proc. Natl. Acad. Sci. USA 2000, 97, 1489–1494.
47. Maudsley, S.; Siddiqui, S.; Martin, B. Systems analysis of arrestin pathway functions. Prog. Mol. Biol. Transl. Sci. 2013, 118, 431–467.
48. Pandey, S.; Kumari, P.; Baidya, M.; Kise, R.; Cao, Y.; Dwivedi-Agnihotri, H.; Banerjee, R.; Li, X.X.; Cui, C.S.; Lee, J.D.; et al. Intrinsic bias at non-canonical, β-arrestin-coupled seven transmembrane receptors. Mol. Cell 2021.
49. Luttrell, L.M.; Ferguson, S.S.; Daaka, Y.; Miller, W.E.; Maudsley, S.; Della Rocca, G.J.; Lin, F.; Kawakatsu, H.; Owada, K.; Luttrell, D.K.; et al. Beta-arrestin-dependent formation of beta2 adrenergic receptor-Src protein kinase complexes. Science 1999, 283, 655–661.
50. Bockaert, J.; Dumuis, A.; Fagni, L.; Marin, P. GPCR-GIP networks: A first step in the discovery of new therapeutic drugs? Curr. Opin. Drug Discov. Dev. 2004, 7, 649–657.
51. Eo, H.S.; Choi, J.P.; Noh, S.J.; Hur, C.G.; Kim, W. A combined approach for the classification of G protein-coupled receptors and its application to detect GPCR splice variants. Comput. Biol. Chem. 2007, 31, 246–256.
52. Hanyaloglu, A.C.; von Zastrow, M. Regulation of GPCRs by endocytic membrane trafficking and its potential implications. Annu. Rev. Pharmacol. Toxicol. 2008, 48, 537–568.
53. Kreienkamp, H.J. Organisation of G-protein-coupled receptor signalling complexes by scaffolding proteins. Curr. Opin. Pharmacol. 2002, 2, 581–586.
54. Fagerberg, L.; Hallström, B.M.; Oksvold, P.; Kampf, C.; Djureinovic, D.; Odeberg, J.; Habuka, M.; Tahmasebpoor, S.; Danielsson, A.; Edlund, K.; et al. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Mol. Cell. Proteom. 2014, 13, 397–406.

55. Maudsley, S.; Patel, S.A.; Park, S.S.; Luttrell, L.M.; Martin, B. Functional signaling biases in G protein-coupled receptors: Game Theory and receptor dynamics. Mini Rev. Med. Chem. 2012, 12, 831–840.
56. Marti-Solano, M.; Crilly, S.E.; Malinverni, D.; Munk, C.; Harris, M.; Pearce, A.; Quon, T.; Mackenzie, A.E.; Wang, X.; Peng, J.; et al. Combinatorial expression of GPCR isoforms affects signalling and drug responses. Nature 2020, 587, 650–656.
57. Maudsley, S.; Martin, B.; Janssens, J.; Etienne, H.; Jushaj, A.; van Gastel, J.; Willemsen, A.; Chen, H.; Gesty-Palmer, D.; Luttrell, L.M. Informatic deconvolution of biased GPCR signaling mechanisms from in vivo pharmacological experimentation. Methods 2016, 92, 51–63.
58. Stoeber, M.; Jullié, D.; Lobingier, B.T.; Laeremans, T.; Steyaert, J.; Schiller, P.W.; Manglik, A.; von Zastrow, M. A Genetically Encoded Biosensor Reveals Location Bias of Opioid Drug Action. Neuron 2018, 98, 963–976.e965.
59. Yang, Y.; Harmon, C.M. Molecular signatures of human melanocortin receptors for ligand binding and signaling. Biochim. Biophys. Acta Mol. Basis Dis. 2017, 1863, 2436–2447.
60. Hilger, D. The role of structural dynamics in GPCR-mediated signaling. FEBS J. 2021, 288, 2461–2489.
61. Ferguson, S.S.; Downey, W.E., 3rd; Colapietro, A.M.; Barak, L.S.; Ménard, L.; Caron, M.G. Role of beta-arrestin in mediating agonist-promoted G protein-coupled receptor internalization. Science 1996, 271, 363–366.
62. Goodman, O.B., Jr.; Krupnick, J.G.; Santini, F.; Gurevich, V.V.; Penn, R.B.; Gagnon, A.W.; Keen, J.H.; Benovic, J.L. Beta-arrestin acts as a clathrin adaptor in endocytosis of the beta2-adrenergic receptor. Nature 1996, 383, 447–450.
63. Gong, H.; Sun, H.; Koch, W.J.; Rau, T.; Eschenhagen, T.; Ravens, U.; Heubach, J.F.; Adamson, D.L.; Harding, S.E. Specific beta(2)AR blocker ICI 118,551 actively decreases contraction through a G(i)-coupled form of the beta(2)AR in myocytes from failing human heart. Circulation 2002, 105, 2497–2503.
64. Seifert, R.; Gether, U.; Wenzel-Seifert, K.; Kobilka, B.K. Effects of guanine, inosine, and xanthine nucleotides on beta(2)-adrenergic receptor/G(s) interactions: Evidence for multiple receptor conformations. Mol. Pharmacol. 1999, 56, 348–358.
65. Carneiro, D.G.; Clarke, T.; Davies, C.C.; Bailey, D. Identifying novel protein interactions: Proteomic methods, optimisation approaches and data analysis pipelines. Methods 2016, 95, 46–54.
66. Martin, B.; Chadwick, W.; Janssens, J.; Premont, R.T.; Schmalzigaug, R.; Becker, K.G.; Lehrmann, E.; Wood, W.H.; Zhang, Y.; Siddiqui, S.; et al. GIT2 Acts as a Systems-Level

Coordinator of Neurometabolic Activity and Pathophysiological Aging. Front. Endocrinol. 2016, 6, 191.

67. van Gastel, J.; Hendrickx, J.O.; Leysen, H.; Martin, B.; Veenker, L.; Beuning, S.; Coppens, V.; Morrens, M.; Maudsley, S. Enhanced Molecular Appreciation of Psychiatric Disorders through High-Dimensionality Data Acquisition and Analytics. Methods Mol. Biol. 2019, 2011, 671–723.
68. Bugge, K.; Brakti, I.; Fernandes, C.B.; Dreier, J.E.; Lundsgaard, J.E.; Olsen, J.G.; Skriver, K.; Kragelund, B.B. Interactions by Disorder—A Matter of Context. Front. Mol. Biosci. 2020, 7, 110.
69. Randhawa, V.; Pathania, S. Advancing from protein interactomes and gene co-expression networks towards multi-omics-based composite networks: Approaches for predicting and extracting biological knowledge. Brief. Funct. Genom. 2020, 19, 364–376.
70. Kalita, B.; Bano, S.; Vavachan, V.M.; Taunk, K.; Seshadri, V.; Rapole, S. Application of mass spectrometry based proteomics to understand diabetes: A special focus on interactomics. Biochim. Biophys. Acta Proteins Proteom. 2020, 1868, 140469.
71. Ahn, S.; Maudsley, S.; Luttrell, L.M.; Lefkowitz, R.J.; Daaka, Y. Src-mediated tyrosine phosphorylation of dynamin is required for beta2-adrenergic receptor internalization and mitogen-activated protein kinase signaling. J. Biol. Chem. 1999, 274, 1185–1188.
72. Rocca, G.J.D.; Maudsley, S.; Daaka, Y.; Lefkowitz, R.J.; Luttrell, L.M. Pleiotropic coupling of G protein-coupled receptors to the mitogen-activated protein kinase cascade. Role of focal adhesions and receptor tyrosine kinases. J. Biol. Chem. 1999, 274, 13978–13984.
73. Luttrell, L.M. ‘Location, location, location’: Activation and targeting of MAP kinases by G protein-coupled receptors. J. Mol. Endocrinol. 2003, 30, 117–126.
74. Sayers, N.; Hanyaloglu, A.C. Intracellular Follicle-Stimulating Hormone Receptor Trafficking and Signaling. Front. Endocrinol. 2018, 9, 653.
75. Stäubert, C.; Schöneberg, T. GPCR Signaling From Intracellular Membranes—A Novel Concept. Bioessays 2017, 39.
76. van Gastel, J.; Leysen, H.; Santos-Otte, P.; Hendrickx, J.O.; Azmi, A.; Martin, B.; Maudsley, S. The RXFP3 receptor is functionally associated with cellular responses to oxidative stress and DNA damage. Aging 2019, 11, 11268–11313.
77. Retamal, J.S.; Ramírez-García, P.D.; Shenoy, P.A.; Poole, D.P.; Veldhuis, N.A. Internalized GPCRs as Potential Therapeutic Targets for the Management of Pain. Front. Mol. Neurosci. 2019, 12, 273.

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