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Current Opinion in
Endocrine and Metabolic Research

Reviews

Subcellular hot spots of GPCR signaling promote vascular inflammation

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Abstract

G-coupled protein receptors (GPCRs) comprise the largest class of druggable targets. Signaling by GPCRs is initiated from subcellular hot spots including the plasma membrane, signalosomes, and endosomes to contribute to vascular inflammation. GPCR-G protein signaling at the plasma membrane causes endothelial barrier disruption and also cross-talks with growth factor receptors to promote proinflammatory signaling. A second surge of GPCR signaling is initiated by cytoplasmic NFκB activation mediated by β-arrestins and CARMA-BCL10-MALT1 signalosomes. Once internalized, ubiquitinated GPCRs initiate signaling from endosomes via assembly of the transforming growth factor-β-activated kinase binding protein-1 (TAB1)-TAB2-p38 MAPK complex to promote vascular inflammation. Understanding the complexities of GPCR signaling is critical for development of new strategies to treat vascular inflammation such as that associated with COVID-19.

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Current Opinion in Endocrine and Metabolic Research 2021, **16**:37–42

This review comes from a themed issue on **G protein-coupled receptors (GPCRs)**

Edited by **Aylin Hanyaloglu** and **Eric Reiter**

For a complete overview see the Issue and the Editorial

Available online 18 August 2020

https://doi.org/10.1016/j.coemr.2020.07.011

Keywords

Arrestins, COVID-19, Endosomes, Endothelial, MALT1, JAK-STAT, NFκB, p38 MAPK.

Abbreviations

angiotensin converting enzyme-2, ACE2; adherens junctions, AJ; angiotensin II type 1 receptor, AT1; caspase recruitment domain-containing protein, CARMA; B-cell lymphoma protein 10, (BCL10); mucosa-associated lymphoid tissue lymphoma translocation protein 1, (MALT1); coronavirus disease of 2019, COVID-19; severe acute respiratory syndrome coronavirus 2, SARS-CoV-2; fibroblast-growth-factor, FGF; G protein-coupled receptor, GPCR; inhibitor of NFκB kinase, IKK; Janus kinase, JAK; mitogen-activated protein kinase, MAPK; neural precursor cell expressed developmentally down-regulated protein 4, NEDD4; nuclear factor kappa-light-chain-enhancer of activated B cells, NFκB; platelet activating factor, PAF; protease-activated receptor-1, PAR1; signal transducer and activator of transcription, STAT; transforming growth factor-α-activated kinase binding protein-1, TAB1.

Introduction

Inflammation is a major component of the innate immune system that enables mammalian cells to respond to tissue damage and pathogens. Acute and chronic inflammation of the vasculature involves a multicellular response that culminates in immune cell recruitment, clearance of damaged cells, tissue repair, and endothelial cell activation [1]. Under normal conditions, endothelial cells form a semipermeable barrier that restricts the movement of fluid and macromolecules into the interstitial space. Endothelial cells also exert anti-inflammatory activities by inhibiting the recruitment and activation of leukocytes under basal conditions [2]. Endothelial activation in response to tissue damage and pathogens is governed by signaling cascades initiated by vasoactive factors, chemokines and cytokines, which are immune cell— and endothelial cell—secreted inflammatory mediators that interact with cell surface receptors and trigger endothelial barrier permeability, gene transcription, and apoptosis. Inflammatory mediators elicit cellular responses via activation of three major signaling pathways including: nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), Janus kinases (JAKs), signal transducer and activator of transcription (STAT), and the p38 mitogen-activated protein kinase (MAPK) signaling pathways [1]. While many inflammatory mediators signal through cytokine receptors, G protein-coupled receptors (GPCRs) also serve as important conduits for generating inflammatory signaling in endothelial cells and other cell types [3].

GPCRs are a diverse family of cell surface transmembrane receptors that respond to various stimuli and promote an array of cellular functions. Upon agonist stimulation, GPCRs undergo conformational changes and facilitate activation of plasma membrane localized heterotrimeric G proteins that initiate intracellular signaling cascades. After activation, GPCRs are phosphorylated by GPCR kinases, bind the multi-functional adaptor β-arrestin proteins, and internalize from the plasma membrane through clathrin-mediated

endocytosis [4]. A second surge of signaling from activated GPCRs occurs within subcellular compartments and is enabled by β-arrestins, which function as scaffolds that nucleate the assembly of signaling complexes [5]. β-arrestin-2 has been shown to mediate pro-inflammatory responses via NFκB activation in the vascular endothelium [6]. An additional trigger of subcellular signaling is induced by ubiquitin covalently linked to activated GPCRs that regulates the recruitment and activation of p38 MAPK signaling complexes on endosomes [7,8]. These studies demonstrate that not only plasma membrane—initiated GPCR signaling but also cytoplasmic- and endosomal-initiated signaling contributes to the orchestration of an effective inflammatory response. In this review, we summarize recent work indicating that in addition to promoting classical inflammatory signaling from the plasma membrane, some GPCRs can fine-tune vascular inflammatory responses by initiating a second surge of signaling from subcellular hot spots.

GPCR-G protein signaling from the plasma membrane initiates endothelial barrier disruption

Disruption of the endothelial barrier results in increased permeability leading to vascular leakage and tissue edema, which are hallmarks of inflammation. Endothelial barrier maintenance is controlled by cell—cell junctions comprising tight junctions and adherens junctions (AJs) that function primarily to maintain barrier integrity. AJs are composed of vascular endothelial cadherin and catenins, which are dynamically regulated by kinases and phosphatases, the dominant type of endothelial cell junctions in vascular beds. Several GPCR agonists including thrombin, histamine, bradykinin, and the platelet activating factor (PAF) promote endothelial barrier disruption via modulation of AJs as well as myosin light-chain kinase activation of actomyosin contractility resulting in alteration of the actin cytoskeleton [9].

A key temporal characteristic of pro-inflammatory GPCR agonists is the rapid activation of G_q and $G_{12/13}$ protein signaling at the plasma membrane that disrupts endothelial cell—cell junctions resulting in transient permeability (Figure 1). Thrombin, a procoagulant serine protease, signals primarily via protease-activated receptor-1 (PAR1), leading to G_q-mediated Ca^{2+} mobilization, protein kinase C activation and $G_{12/13}$-dependent RhoA signaling to promote AJ disassembly and barrier disruption [10]. Histamine acting through the H1 histamine receptor causes increases in intracellular Ca^{2+} and c-Src activation [11], whereas bradykinin activation of the bradykinin B2 receptor results in Ca^{2+} mobilization and endothelial nitric oxide synthase activity [12]. PAF signals via the PAF receptor, which couples to G_q and Rac1 activation and promotes reorganization of the actin cytoskeleton and endothelial barrier disruption [13]. Thus, the initiation of GPCR inflammatory signaling occurs at the plasma membrane via rapid coupling to heterotrimeric G proteins resulting in transient alteration of endothelial barrier permeability.

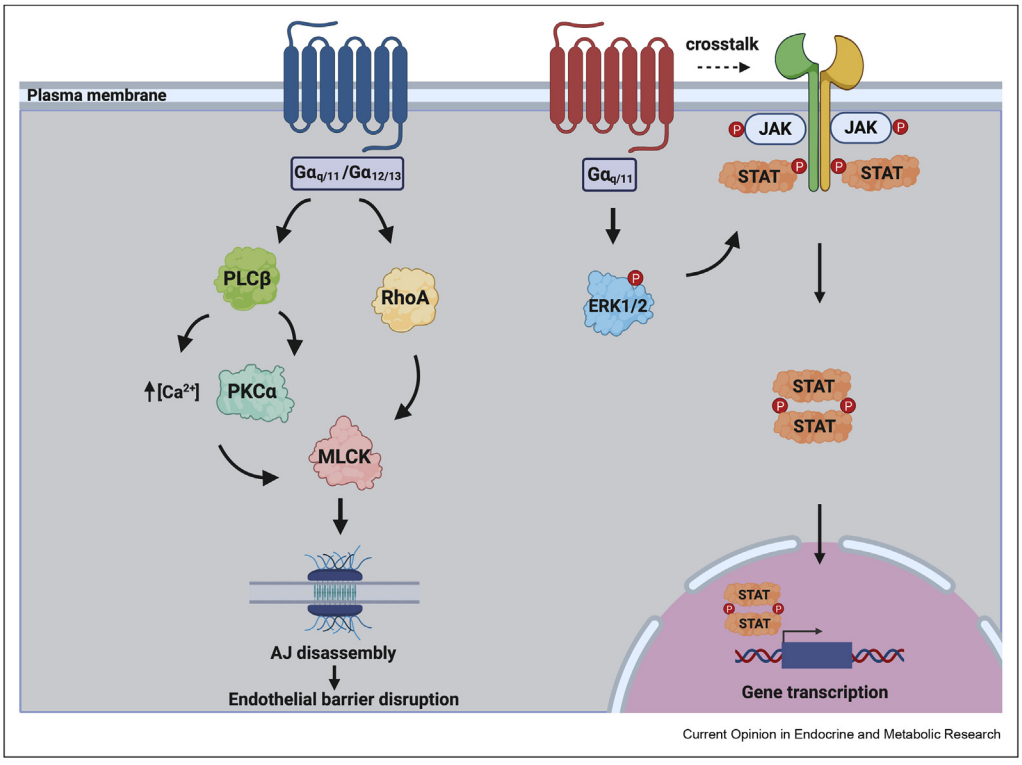
GPCRs transactivate JAK-STAT inflammatory signaling at the plasma membrane

Of the key inflammatory pathways, activation of the JAK-STAT pathway is the most proximal to the plasma membrane with a simple architecture that permits direct communication with the nucleus. A wide array of cytokine and growth factor receptors directly activate JAK-STAT pathways, whereas GPCRs appear to signal indirectly to the JAK-STAT pathway via crosstalk with other receptors in the vascular endothelium (Figure 1). In adddition, JAK interacts directly with the GPCR angiotensin II type 1 receptor (AT1 receptor) and PAF receptor in smooth muscle and other cell types [14]. Classically, JAK proteins associate with the cytoplasmic tail of ligand-bound cytokine and growth factor receptors to trigger phosphorylation of STAT family transcription factors, resulting in dimerization, subsequent nuclear translocation and STAT-dependent gene expression that promotes apoptosis, cell migration, and differentiation [15]. However, bradykinin activation of B2 receptor stimulates extracellular signal regulated kinases-1/2-mediated STAT activation that bridges a positive regulatory loop with the fibroblast growth factor (FGF-2)—FGR1 axis to stimulate endothelial cell barrier disruption and migration [16]. Interestingly, new work suggests that complement factors promote vascular inflammation via GPCR signaling. Activation of the complement pathway during vascular injury results in the release of complement activated peptides C3a and C5a, which signal through the anaphylatoxin C3a and C5a GPCRs expressed in endothelial cells. In recent work, C3a and C5a stimulated endothelial cells exhibited enhanced C3a and C5a receptor expression and a host of pro-inflammatory responses including lymphocyte activation, infiltration, and cytokine production that was diminished by a JAK inhibitor [17], implicating a role for the JAK-STAT inflammatory signaling pathway. Although these GPCRs appear to initiate JAK-STAT activation from the cell surface, other receptors may require endocytosis for coupling to this inflammatory pathway.

GPCR activation of NFκB inflammatory signaling via signalosomes

NFκB is a ubiquitously expressed family of inducible transcription factors that regulate inflammation, cell proliferation, cell survival, and cell death [18,19]. NFκB-transcriptionally activated genes include pro-inflammatory cytokines, chemokines, apoptotic factors, and adhesion molecules that facilitate immune cell

Figure 1



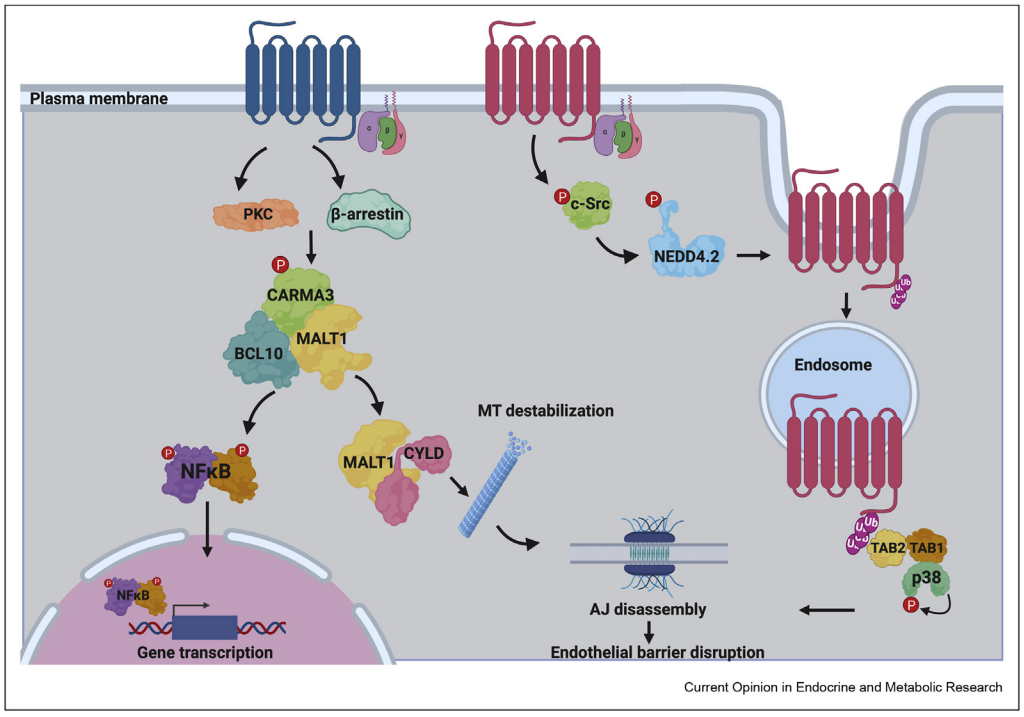
GPCR inflammatory signaling from the plasma membrane. Activated GPCRs couple to G_q and/or $G_{12/13}$ to induce phospholipase C-β (PLCβ)–induced Ca^{2+} mobilization, protein kinase C (PKC) activation, and RhoA signaling. These signaling cascades converge on myosin light-chain kinase (MLCK) and result in alterations in the actin cytoskeleton, adherens junctions (AJs), and consequent endothelial barrier disruption. In addition, some GPCRs signal via G_q-extracellular signal regulated kinases-(ERK)1/2 to transactivate growth factor receptors to stimulate activation of the janus kinase (JAK) and signal transducer and activator of transcription proteins (STAT) pathway to modulate transcriptional proinflammatory responses. ERK, extracellular signal regulated kinase; JAK, janus kinase; PKC, protein kinase C; PLC, phospholipase C; STAT, signal transducer and activator of transcription.

recruitment. There are five NFκB members expressed in mammalian cells and five inhibitory proteins that regulate classical and nonclassical NFκB activation. Under basal conditions, inhibitory proteins sequester NFκB dimers in the cytoplasm; however, upon stimulation inhibitory proteins are phosphorylated, ubiquitinated, and degraded by the proteasome, resulting in NFκB activation, translocation to the nucleus, and gene transcription. The pathways by which different receptors link to NFκB activation in distinct cell types are diverse, complex and regulated by scaffolds that form signalosomes, which are multifunctional cytoplasmic protein complexes.

β-arrestins regulate GPCR-stimulated NFκB activity in various cell types [20]; however, new work suggests that the major driver of NFκB activation utilized by GPCRs is the caspase recruitment domain—containing proteins known as CARMA. CARMA associates with two signaling proteins B-cell lymphoma protein 10 (BCL10) and mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) (Figure 2). Activation of the CARMA-BCL10-MALT1 (CBM) complex is initiated by PKC-dependent phosphorylation of CARMA [21], which nucleates complex formation with the constitutively associated BCL10 and MALT1 proteins and contributes to the regulation of the inhibitor of NFκB kinase (IKK) complex activity through polyubiquitination [22]. Interestingly, CBM complexes can mature into higher-order oligomers that generate 'hubs' of signalosomes for localized and sustained enhancement of NFκB activity in the cytoplasm [23].

Several pro-inflammatory endothelial GPCRs agonists stimulate NFκB activation through the CARMA3-BCL10-MALT1 complex including thrombin, angiotensin II, and CXCL8 or interleukin-8 [24—26] Thrombin activation of PAR1 induces PKC-dependent NFκB activation through CARMA3-BCL10-MALT1 complex engagement of IκB degradation and release of active NFκB in endothelial cells (Figure 2) [25]. NFκB signaling promotes vascular cell adhesion molecule-1 and intracellular adhesion molecule-1 expression and monocyte adhesion after thrombin stimulation.

Figure 2



GPCR-mediated proinflammatory signaling via signalosomes and endosomes. Upon activation, some GPCRs signal via G_q, PKC, and β-arrestins to promote CARMA3 phosphorylation, which triggers the assembly of CARMA3-BCL10-MALT1 (CBM) signalosomes. These complexes recruit other signaling components and ultimately lead to phosphorylation and nuclear translocation of the transcription factor NFκB. The MALT1 protease activity of the complex can cleave the microtubule stabilizing deubiquitinase cylindromatosis (CYLD), resulting in endothelial barrier disruption. A subset of other GPCRs trigger ubiquitin-driven p38 proinflammatory signaling from endosomes through a noncanonical pathway mediated by transforming growth factor-β activating protein binding protein-1 (TAB1) and TAB2. Ubiquitin-induced p38 MAPK signaling promotes endothelial barrier disruption.

Moreover, thrombin-induced CBM complex formation requires β-arrestin-2, suggesting that β-arrestin-2 may function as a scaffold to facilitate nucleation of the CBM complex. Thrombin activation of the CBM complex also results in an additional MALT1-dependent response resulting in proteolytic degradation of the microtubule stabilizing protein cylindromatosis that triggers endothelial cell retraction and acute barrier permeability (Figure 2) [27]. Consistent with these findings, a recent study demonstrated that histamine acting via the H1 histamine receptor increases MALT1 activity and is required for histamine-induced endothelial barrier permeability *in vitro* and *in vivo* [28]. Together, these studies suggest that endothelial GPCRs utilize CBM for dual inflammatory functions including NFκB activation and endothelial barrier disruption.

GPCRs stimulate ubiquitin-driven p38 MAPK activation on endosomes

The p38 MAPK signaling cascade is a key mediator of inflammation [29] and known to regulate stress- and inflammation-induced cellular and transcriptional responses in various cell types [30,31]. New emerging data suggest that like CBM, p38 MAPK has dual inflammatory functions controlling both gene transcription and cellular responses such as endothelial barrier permeability. All four p38 isoforms (α, β, δ, and γ) are activated by the canonical 3-tiered kinase cascade mediated by upstream MAP2Ks and MAP3Ks [32,33]. However, a noncanonical pathway of p38 MAPK activation is prevalent and utilized by cytokines and GPCR agonists via transforming growth factor-β-activated kinase binding protein-1 (TAB1). TAB1 directly binds the p38α isoform resulting in autophosphorylation and activation that bypasses the requirement for upstream MAPK2s and MAP3Ks (Figure 2) [7,34,35]. Thus, GPCRs can activate different subcellular populations of p38 MAPK that preferentially phosphorylate cytoplasmic and/or nuclear substrates to regulate inflammatory gene expression, apoptosis, and endothelial barrier permeability [31].

A major difference between the canonical and noncanonical activation of p38 MAPK signaling is the subcellular localization of its activity in the nucleus *versus* the cytoplasm. Ubiquitination of thrombin-activated PAR1 is mediated by the neural precursor cell expressed developmentally downregulated protein 4 (NEDD4) E3 ubiquitin ligase and initiated at the cell surface by G protein signaling; however, activated ubiquitinated PAR1-TAB1-TAB2 complex accumulates

on endosomes and propagates prolonged p38 MAPK activity in the cytoplasm [7]. Ubiquitin-driven p38 MAPK signaling induced by PAR1 promotes endothelial barrier permeability *in vitro*, and p38 MAPK is required for PAR1-stimulated vascular leakage *in vivo* [7]. ADP stimulation of the P2Y1 receptor also requires ubiquitination, TAB1, and TAB2 to activate endosomal p38 MAPK signaling, indicating that this pathway is not limited to PAR1. In fact, multiple endothelial GPCRs agonists including histamine and prostaglandins also require TAB1 and TAB2 or TAB3 to stimulate p38 MAPK-dependent induction of interleukin-6 production in various types of endothelial cells derived from different vascular beds [36], suggesting that TAB1-dependent p38 MAPK activation is a universal pathway utilized by GPCRs.

A critical role for ubiquitin as a trigger for GPCR-induced p38 MAPK inflammatory signaling is further supported by recent work that has unveiled the mechanism of NEDD4 E3 ligase activation induced by GPCRs. In this work, activated PAR1 was shown to stimulate NEDD4 E3 ligase activity through c-Src-dependent phosphorylation of a tyrosine residue within the 2,3-linker peptide of WW2 and WW3 of NEDD4 to promote p38 MAPK signaling and endothelial barrier disruption [8]. C-Src was also shown to function as a key regulator of NEDD4 activity and ubiquitin-driven p38 MAPK inflammatory signaling induced by activated P2Y1 receptor.

Interestingly, both p38 MAPK and GPCRs have been implicated in the progression of the coronavirus disease of 2019 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which leads to massive inflammation in the lung and heart. The exact cause of inflammation is not known. SAR2-CoV-2 binds to angiotensin converting enzyme-2 expressed on cells highly abundant in the lung and heart. Angiotensin converting enzyme-2 is important for controlling the levels of angiotensin II, which signals through AT1 to promote inflammatory signaling including p38 MAPK activation [37]. In addition, a human-SARS-CoV-2-host interactome screen revealed that PAR2 associates with SARS-CoV-2 via an accessory protein in the region Ofr9c [38]. PAR2 also plays a pivotal role in vascular inflammation [39] and can signal via p38 MAPK [40]. Given the lack of clinically efficacious drugs currently available to treat the coronavirus disease of 2019, small molecule inhibitors targeting certain GPCRs and/or p38 MAPK might be considered for early phase clinical trials.

Conclusions

Vascular inflammation results from subcellular hot spots of GPCR signaling initiated at the plasma membrane, cytoplasmic signalosomes, and, more recently, in endosomal compartments. Plasma membranelocalized GPCR signaling engages heterotrimeric G proteins, and classical signaling cascades to promote proinflammatory signaling resulting in endothelial barrier disruption. A second mode of plasma membrane–localized signaling occurs via transactivation of growth factor receptors causing JAK-STAT signaling, transcriptional activity, and inflammatory responses. In addition, GPCRs utilize scaffolds that facilitate the assembly of multiprotein complexes in the cytoplasm to promote NFκB activation induced by β-arrestins and CARMA-BCL10-MALT1 signalosomes that accumulate in localized cytoplasmic hubs that sustained NFκB activity. An additional type of GPCR inflammatory signaling occurs at endosomes and is driven by ubiquitin covalently attached to the receptor and functions to nucleate the assembly of TAB1-TAB2-p38 MAPK signaling complex. Cleary, future work is needed to gain insights into the molecular architecture and structure of GPCR signaling complexes to identify new targets and strategies for development of drugs that are more effective to treat vascular inflammation with adverse side effects.

Funding

This work was supported by National Institutes of Health / National Institute of General Medical Sciences(R35 GM127121), NIH / NIGMS (K12 GM068524), NIH / National Heart, Lung, and Blood Institute (T32 HL007444) and Burroughs Welcome Fund Postdoctoral Enrichment Program (1019868).

Conflict of interest statement

Nothing declared.

Acknowledgements

The authors thank members of the Trejo laboratory of suggestions and advice.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Chen L, *et al.*: **Inflammatory responses and inflammation-associated diseases in organs**. *Oncotarget* 2018, **9**: 7204–7218.
2. Pober JS, Sessa WC: **Inflammation and the blood microvascular system**. *Cold Spring Harb Perspect Biol* 2014, **7**:a016345.
3. Sun L, Ye RD: **Role of G protein-coupled receptors in inflammation**. *Acta Pharmacol Sin* 2012, **33**:342–350.
4. Gurevich VV, Gurevich EV: **GPCR signaling regulation: the role of GRKs and arrestins**. *Front Pharmacol* 2019, **10**:125.
5. Hanyaloglu AC: **Advances in membrane trafficking and endosomal signaling of G protein-coupled receptors**. *Int Rev Cell Mol Biol* 2018, **339**:93–131.
6. Freedman NJ, Shenoy SK: **Regulation of inflammation by beta-arrestins: not just receptor tales**. *Cell Signal* 2018, **41**: 41–45.

7. Grimsey NJ, *et al.*: **Ubiquitin plays an atypical role in GPCR-induced p38 MAP kinase activation on endosomes**. *J Cell Biol* 2015, **210**:1117–1131.

8. ** Grimsey NJ, *et al.*: **A tyrosine Switch on NEDD4-2 E3 ligase transmits GPCR inflammatory signaling**. *Cell Rep* 2018, **24**: 3312–3323 e5.
This study shows that GPCRs stimulate activation of the NEDD4-2 E3 ubiquitin ligase via c-Src to induce endothelial p38 proinflammatory signaling. c-Src phosphorylates NEDD4-2 at tyrosine-485, releasing the autoinhibitory linker peptide that is critical for enhancing E3 ligase activity, and provides mechanistic insight of how GPCRs activate E3 ubiquitin ligases in mammalian cells.

9. Dalal PJ, Muller WA, Sullivan DP: **Endothelial cell calcium signaling during barrier function and inflammation**. *Am J Pathol* 2020, **190**:535–542.

10. Komarova YA, Mehta D, Malik AB: **Dual regulation of endothelial junctional permeability**. *Sci STKE* 2007, **2007**:re8.

11. Guo M, *et al.*: **VE-cadherin and beta-catenin binding dynamics during histamine-induced endothelial hyperpermeability**. *Am J Physiol Cell Physiol* 2008, **294**:C977–C984.

12. Leeb-Lundberg LM: **Bradykinin specificity and signaling at GPR100 and B2 kinin receptors**. *Br J Pharmacol* 2004, **143**: 931–932.

13. Knezevic II , *et al.*: **Tiam1 and Rac1 are required for platelet-activating factor-induced endothelial junctional disassembly and increase in vascular permeability**. *J Biol Chem* 2009, **284**: 5381–5394.

14. Ritter SL, Hall RA: **Fine-tuning of GPCR activity by receptor-interacting proteins**. *Nat Rev Mol Cell Biol* 2009, **10**:819–830.

15. Morris R, Kershaw NJ, Babon JJ: **The molecular details of cytokine signaling via the JAK/STAT pathway**. *Protein Sci* 2018, **27**:1984–2009.

16. Terzuoli E, *et al.*: **Bradykinin B2 receptor contributes to inflammatory responses in human endothelial cells by the transactivation of the fibroblast growth factor receptor FGFR-1**. *Int J Mol Sci* 2018, **19**:2638.

17. * Shivshankar P, *et al.*: **In response to complement anaphylatoxin peptides C3a and C5a, human vascular endothelial cells migrate and mediate the activation of B-cells and polarization of T-cells**. *Faseb J* 2020, **34**:7540–7560.
This study showed that completent activation peptides C3a and C5a which signal through GPCRs modulate lymphocyte function via activation of vascular endothelial cells.

18. Liu T, *et al.*: **NF-kappaB signaling in inflammation**. *Signal Transduct Target Ther* 2017, **2**:17023.

19. Zhang Q, Lenardo MJ, Baltimore D: **30 Years of NF-kappaB: a blossoming of relevance to human pathobiology**. *Cell* 2017, **168**:37–57.

20. van Gastel J, *et al.*: **Beta-arrestin based receptor signaling paradigms: potential therapeutic targets for complex age-related disorders**. *Front Pharmacol* 2018, **9**:1369.

21. Zhang S, Lin X: **CARMA3: scaffold protein involved in NF-kappaB signaling**. *Front Immunol* 2019, **10**:176.

22. Juilland M, Thome M: **Holding all the CARDs: how MALT1 controls CARMA/CARD-Dependent signaling**. *Front Immunol* 2018, **9**:1927.

23. ** David L, *et al.*: **Assembly mechanism of the CARMA1-BCL10-MALT1-TRAF6 signalosome**. *Proc Natl Acad Sci U S A* 2018, **115**:1499–1504.
Using biophysical approaches this work studied the assembly of the CARMA1-BCL10- MALT1-TRAF6 complex and showed that CARMA1 nucleates BCL10 filament formation resulting in MALT1 dimerization and activation, whereas TRAF6 is incorporated into the complex cooperatively.

24. Martin D, Galisteo R, Gutkind JS: **CXCL8/IL8 stimulates vascular endothelial growth factor (VEGF) expression and the autocrine activation of VEGFR2 in endothelial cells by activating NFkappaB through the CBM (Carma3/Bcl10/Malt1) complex**. *J Biol Chem* 2009, **284**:6038–6042.

25. Delekta PC, *et al.*: **Thrombin-dependent NF-{kappa}B activation and monocyte/endothelial adhesion are mediated by the CARMA3.Bcl10.MALT1 signalosome**. *J Biol Chem* 2010, **285**: 41432–41442.

26. McAllister-Lucas LM, *et al.*: **CARMA3/Bcl10/MALT1-dependent NF-kappaB activation mediates angiotensin II-responsive inflammatory signaling in nonimmune cells**. *Proc Natl Acad Sci U S A* 2007, **104**:139–144.

27. Klei LR, *et al.*: **MALT1 protease activation triggers acute disruption of endothelial barrier integrity via CYLD cleavage**. *Cell Rep* 2016, **17**:221–232.

28. * Alfano DN, *et al.*: **MALT1 protease plays a dual role in the allergic response by acting in both mast cells and endothelial cells**. *J Immunol* 2020, **204**:2337–2348.
This study showed that in addition to mediating allergic responses in mast cells, MALT1 has a pivotal role in promoting endothelial inflammatory responses induced by histamine, a mast cell vasoactive substance.

29. Gupta J, Nebreda AR: **Roles of p38alpha mitogen-activated protein kinase in mouse models of inflammatory diseases and cancer**. *FEBS J* 2015, **282**:1841–1857.

30. Martinez-Limon A, *et al.*: **The p38 pathway: from biology to cancer therapy**. *Int J Mol Sci* 2020, **21**:1913.

31. Cuadrado A, Nebreda AR: **Mechanisms and functions of p38 MAPK signalling**. *Biochem J* 2010, **429**:403–417.

32. Remy G, *et al.*: **Differential activation of p38MAPK isoforms by MKK6 and MKK3**. *Cell Signal* 2010, **22**:660–667.

33. Brancho D, *et al.*: **Mechanism of p38 MAP kinase activation in vivo**. *Genes Dev* 2003, **17**:1969–1978.

34. Ge B, *et al.*: **MAPKK-independent activation of p38alpha mediated by TAB1-dependent autophosphorylation of p38alpha**. *Science* 2002, **295**:1291–1294.

35. De Nicola GF, *et al.*: **The TAB1-p38alpha complex aggravates myocardial injury and can be targeted by small molecules**. *JCI Insight* 2018, **3**, e121144.

36. Grimsey NJ, *et al.*: **G protein-coupled receptors activate p38 MAPK via a non canonical TAB1-TAB2- and TAB1-TAB3-dependent pathway in endothelial cells**. *J Biol Chem* 2019, **294**:5867–5878.

37. Park JK, *et al.*: **p38 mitogen-activated protein kinase inhibition ameliorates angiotensin II-induced target organ damage**. *Hypertension* 2007, **49**:481–489.

38. ** Gordon DE, *et al.*: **A SARS-CoV-2 protein interaction map reveals targets for drug repurposing**. *Nature* 2020, **583**:459–468.
This study identified several potential druggable targets by generating a human-SARS-CoV-2 protein interaction map that includes the GPCR PAR2. This work reveals the identification of new targets and strategies for developing drugs with clinically efficacious antiviral activity.

39. Hara T, *et al.*: **Protease-activated receptor-2 plays a critical role in vascular inflammation and atherosclerosis in apolipoprotein E-deficient mice**. *Circulation* 2018, **138**:1706–1719.

40. Pan SL, *et al.*: **The p38 mitogen-activated protein kinase pathway plays a critical role in PAR2-induced endothelial IL-8 production and leukocyte adhesion**. *Shock* 2008, **30**:496–502.