

Beyond canonical GPCR: emerging roles of seven transmembrane proteins in metabolic control – insights from GPR180: A review

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G protein-coupled receptors (GPCRs) are traditionally defined by their seven-transmembrane (7TM) domain architecture and ability to activate heterotrimeric G proteins. However, accumulating evidence challenges this structure-centric view, revealing a growing class of 7TM proteins that operate through non-canonical mechanisms. GPR180, initially annotated as an orphan GPCR based on predicted 7TM structure, has emerged as a paradigmatic example of this divergence. It lacks demonstrable G protein coupling and instead regulates metabolic function through atypical signalling pathways that influence mitochondrial bioenergetics, lipid handling, and cellular phenotype across multiple metabolic tissues. In adipose tissue, GPR180 controls adipocyte metabolic capacity and thermogenic programming, whereas in the liver, it modulates lipid homeostasis. Importantly, experimental topology analyses reveal inverted membrane orientation, distinguishing GPR180 from *bona fide* GPCRs despite shared 7TM architecture. Recent structural and functional analyses place GPR180 within the GOST (GOLD-domain 7TM) protein family; here, we propose a metabolically specialized GOST subclass, defined by regulation of mitochondrial bioenergetics and metabolic cell identity rather than classical G protein signalling. Together, these findings argue that GPR180 does not operate as a classical GPCR and highlight the need for functional criteria that extend beyond 7TM architecture when defining receptor identity. More broadly, GPR180 exemplifies how atypical 7TM proteins integrate metabolic state and cellular context to shape signalling output, providing a conceptual framework to systematically identify additional GOST family members with organelle-centred, non-canonical metabolic functions.

Keywords: atypical receptors, GPR180, GOST proteins, metabolism, adipocytes, liver

G protein-coupled receptors (GPCRs) are a large family of receptors characterized by a conserved architecture of seven transmembrane (7TM) α -helices that span the plasma membrane. GPCRs are significant regulators of metabolic homeostasis. They are traditionally viewed as mediators of rapid cellular responses through canonical second-messenger pathways, such as cAMP and intracellular Ca^{2+} (Zhang et al. 2024). While this paradigm has successfully explained acute metabolic effects, it offers a limited

framework for understanding how GPCR signalling can drive sustained changes in cellular metabolism, organelle function, and long-term metabolic cell identity. Emerging evidence indicates that a subset of GPCRs operates through non-canonical, or atypical signalling modes, engaging mechanisms that affect mitochondrial metabolism, inter-organelle organization, and transcriptional programs rather than acting solely as triggers of immediate signal transduction (Crilly and Puthenveedu 2021; Nurnberg et

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al. 2024; Austin *et al.* 2025; Pan *et al.* 2025). Metabolite-sensing GPCRs (e.g., free fatty acids receptors) have been increasingly recognized for their roles in physiology and metabolic disease, further highlighting the diverse mechanisms by which GPCRs influence whole-body metabolism (Blad *et al.* 2012). However, in most cases, these receptors still conform to canonical G protein-second messenger models, underscoring that 7TM architecture alone does not predict whether metabolism-related receptors will engage classical or non-canonical signalling modes. Collectively, these observations challenge the traditional view of GPCR biology by revealing how GPCR-associated signalling can be coupled to the structural and functional remodelling of intracellular organelles that shape cellular metabolism.

In this context, the orphan receptor G protein-coupled receptor 180 (GPR180) has emerged as a compelling example of a receptor implicated in the regulation of cellular energy metabolism, including

mitochondrial activity and nutrient handling across tissues (Balazova *et al.* 2021; Yoshida *et al.* 2023). By exhibiting features that extend beyond classical GPCR signalling paradigms, GPR180 provides a specific framework to illustrate how atypical GPCRs can influence metabolic signalling networks and long-term metabolic adaptation. In this review, we summarize current knowledge on GPR180 biology and use it as a case study to highlight the broader principles by which atypical GPCR function in metabolic control.

From linear cascades to metabolic adaptation: expanding GPCR signalling concepts

Traditionally, GPCR signalling is viewed as a mostly linear process, in which ligand binding at the plasma membrane triggers short-term intracellular responses via heterotrimeric G proteins and second messengers, which terminate once the signalling intermediates

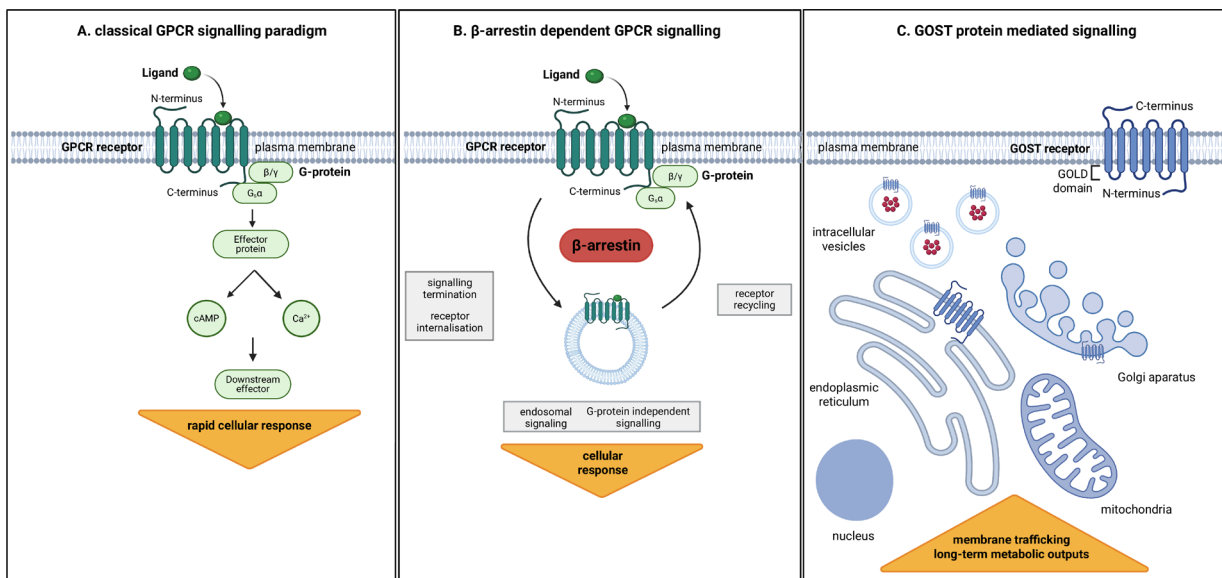


Figure 1. Distinct functional paradigms of seven-transmembrane proteins. **(A)** Classical GPCR signalling. Canonical G protein-coupled receptors (GPCRs) reside in the plasma membrane and are activated by extracellular ligands. Ligand binding induces conformational changes that promote coupling to heterotrimeric G proteins ($G\alpha$ and $G\beta\gamma$), leading to the production of second messengers such as cAMP or Ca^{2+} and the activation of downstream effector proteins. These signalling cascades typically generate rapid cellular responses. **(B)** Spatially organized GPCR signalling. In addition to classical plasma membrane signalling, many GPCRs can signal from intracellular compartments. Following ligand activation, receptors recruit β -arrestins, which promote receptor internalization and trafficking to endosomes. Within these compartments, GPCRs can continue to signal through G protein-independent or sustained pathways before being recycled back to the plasma membrane. This spatial organization of signalling expands the diversity and duration of GPCR-mediated cellular responses. **(C)** GOLD-domain seven-transmembrane (GOST) proteins. Members of the GOST family share a seven-transmembrane architecture but exhibit an inverted membrane topology relative to canonical GPCRs and contain luminal GOLD (Golgi dynamics) domains. These proteins localize to both the plasma membrane and intracellular membranes, such as the endoplasmic reticulum and the Golgi apparatus, and are primarily involved in membrane trafficking. Emerging evidence suggests that some GOST proteins, including GPR180, may additionally influence cellular metabolism and long-term metabolic phenotypes through mechanisms distinct from classical G protein signalling. Abbreviations: cAMP – cyclic adenosine monophosphate; GOLD – Golgi dynamics; GOST – GOLD-domain seven transmembrane; GPCR – G protein Coupled Receptor; GPR180 – G protein Coupled Receptor 180.

decline (Figure 1A). While this concept has been highly successful in explaining acute physiological responses, accumulating evidence across multiple systems suggests that it captures only a subset of GPCR functions. GPCRs can engage spatially restricted and temporally prolonged signalling modes that are mechanistically distinct from classical G protein-second messenger coupling, enabling receptor activity to persist beyond the initial ligand-receptor interaction.

Pioneering studies have demonstrated that GPCRs continue to signal following internalization, with receptors such as the β_2 -adrenergic receptor generating sustained downstream responses from endosomal compartments rather than exclusively at the cell surface (Irannejad et al. 2013; Tsvetanova and von Zastrow 2014). These observations established receptor trafficking and subcellular localization as integral determinants of signalling output, fundamentally challenging the notion that GPCR signalling is inherently transient or spatially uniform. Such spatial encoding of signalling allows localized effector engagement and sustained modulation of downstream pathways, extending GPCR influence to timescales far beyond acute stimulation.

Beyond receptor trafficking, GPCR signalling has also been shown to interface with intracellular organelles and metabolic processes through mechanisms not readily explained by canonical second-messenger models. Components of the G protein signalling machinery have been detected at intracellular membranes, such as endosomes, mitochondria, the Golgi apparatus, and nuclear membranes, where they can locally regulate bioenergetic pathways and organelle function (Lyssand and Bajjalieh 2007; Crilly and Puthenveedu 2021). Moreover, GPCR activation can induce sustained transcriptional and metabolic reprogramming, influencing cellular phenotypes over hours to days rather than minutes (Wehbi et al. 2013; Kwon et al. 2022). Together, these findings suggest that GPCR-related signalling may operate as an initial trigger in long-term adaptive responses, blurring the traditional boundary between membrane-proximal signalling and nuclear or metabolic regulation.

An additional layer of complexity arises from GPCR signalling promiscuity, in which individual receptors can interact with multiple signalling partners or pathways in a context-dependent manner. Such flexibility enables the same receptor to generate distinct outcomes depending on cell type, subcellular localization, or metabolic state, further expanding the diversity and durability of GPCR-driven cellular responses (Wootten et al. 2018; Zhang et al. 2024).

In metabolic tissues, such signalling properties are particularly important. Metabolic homeostasis depends not only on the rapid regulation of enzyme activity and ion fluxes but also on coordinated regulation of substrate utilization and energy production, as well as on the integration of metabolic signals with cellular specialization and identity (Prentki et al. 2013; Rui 2014). These processes inherently operate over extended timescales compared to acute hormone signalling. GPCRs capable of engaging atypical signalling modes – as outlined in Box 1 – are therefore well positioned to integrate extracellular signals with persistent changes in metabolic function. Rather than acting as transient “on-off” switches, these signalling systems can shape how cells adapt to chronic nutrient exposure, hormonal imbalance, or metabolic stress. This expanded view of GPCR signalling provides a conceptual basis for understanding how specific receptors may regulate long-term aspects of metabolic function, including processes traditionally attributed to intracellular signalling networks or transcriptional regulators rather than surface receptors. It also offers a framework for examining individual GPCRs whose functions extend beyond classical signalling paradigms. Within this context, GPR180 emerges as a molecular example whose biology challenges conventional definitions of GPCR function and classification.

Accumulating evidence indicates that 7TM architecture alone does not define the canonical function of G protein-coupled receptors. Several receptors with GPCR-like features signal independently of classical heterotrimeric G proteins or engage alternative, non-canonical mechanisms such as β -arrestin scaffolding (Figure 1B), ligand scavenging, or direct regulation of cell adhesion and structural functions (Rajagopal et al. 2010; Bonecchi et al. 2014). Adhesion GPCRs, a large family of 7TM receptors with extended extracellular domains and complex proteolytic processing, exemplify this diversity by mediating mechanosensory, cell-cell or cell-matrix interactions through modes of activation that are only partially dependent on classical G protein coupling (Lala and Hall 2022). GPR180 fits within this emerging class of atypical 7TM proteins (Table 1), whose biological roles extend beyond conventional GPCR signalling paradigms.

GPR180: an atypical receptor at the interface of metabolism and cellular function

GPR180 was initially identified as the intimal thickness receptor (ITR) in vascular smooth muscle cells, based on its upregulation following vascular

injury and its association with intimal thickening. It was annotated as an orphan G protein-coupled receptor due to the presence of predicted 7TM domains (Tsukada *et al.* 2003), though subsequent studies have shown that it does not function as a classical GPCR (Balazova *et al.* 2021; Yoshida *et al.* 2023; Mitrovic *et al.* 2024). Despite this, GPR180 has emerged as a significant modulator of cellular metabolism and identity in multiple tissues. It is expressed in various tissues, including adipose tissue (Balazova *et al.* 2021; Zhu *et al.* 2025), pancreas, skeletal muscle (Tsukada *et al.* 2003), and liver (Tsukada *et al.* 2003; Zhang *et al.* 2023), where it influences energy homeostasis, mitochondrial function, and long-term metabolic adaptation (Balazova *et al.* 2021; Zhang *et al.* 2023; Zhu *et al.* 2025). Human genetic studies, including GWAS, have

Box 1: Hallmarks of atypical GPCR signalling in metabolic cells

Atypical GPCR signalling refers to modes of GPCR action that extend beyond the classical paradigm of rapid, plasma membrane-restricted activation of second-messenger pathways such as cAMP or intracellular Ca^{2+} . Rather than replacing canonical signalling, these mechanisms broaden the functional repertoire of GPCRs in metabolic cells. Key hallmarks include:

- **Non-canonical signalling outputs**
GPCR activation can regulate cellular processes not traditionally considered GPCR endpoints, including mitochondrial metabolism, bioenergetic state, redox balance, and transcriptional programs linked to metabolic adaptation. These outputs may also arise from proteins historically annotated as GPCRs but whose mechanisms diverge from classical G protein signalling, such as GPR180.
- **Spatially compartmentalized signalling**
GPCR signalling can originate from or be propagated at intracellular locations, including endosomes, mitochondria and specialized membrane contact sites, enabling localized control of organelle function and inter-organelle communication.
- **Sustained and long-term effects**
In contrast to transient second-messenger responses, atypical GPCR signalling can drive persistent metabolic remodeling, influence differentiation state, and contribute to the maintenance or alteration of metabolic cell identity.
- **Context-dependent and cell-specific signalling (GPCR promiscuity)**
Individual receptors can engage multiple signalling partners or pathways depending on cell type, receptor expression level, metabolic state, or subcellular localization. This flexibility enables a single receptor to generate distinct outcomes in different metabolic contexts.

Together, these features highlight how GPCRs can act as integrators of extracellular cues with intracellular metabolic organization and long-term cellular fate. Although GPR180 does not meet current criteria for a classical GPCR, it exemplifies several of these characteristics, providing a valuable model to explore how atypical GPCR signalling interfaces with cellular metabolic regulation.

Table 1
List of atypical seven-transmembrane receptors

Receptor	7TM architecture	G protein coupling	Principal non-canonical mechanism	Major tissues/function	Reference
ACKR2 (GPR182)	Yes	No	Chemokine scavenging; gradient modulation	Endothelium, leukocytes	Bonecchi <i>et al.</i> 2014
ACKR3 (CXCR7)	Yes	No	β -arrestin-dependent endocytic/scavenger function	Vascular, immune regulation	Rajagopal <i>et al.</i> 2010
ADGRE2 (CD97)	Yes (complex N-termini)	family-dependent; often conditional or limited	Adhesion, mechanosensing, scaffold interactions	Development, immunity, cancer, tissue morphogenesis	Bassilana <i>et al.</i> 2019
AdipoR1/AdipoR2	Yes (inverted topology)	No	AMPK activation; ceramidase-related function	Liver, muscle, adipose; energy metabolism	Yamauchi <i>et al.</i> , 2003
AT1R (biased signalling)	Yes	Yes/No*	β -arrestin-mediated kinase pathway	Cardiovascular regulation	Wei <i>et al.</i> 2003
GPR180	Yes (inverted topology)	not demonstrated	Atypical metabolic regulation; TGF β -SMAD associations	Adipose, liver, metabolic regulation	Balazova <i>et al.</i> 2021; Mitrovic <i>et al.</i> 2024

*Biased signalling indicates engagement of non-G protein pathways even by classical GPCRs. Abbreviations: ACKR2 – Atypical Chemokine Receptor 2; ACKR3 – Atypical Chemokine Receptor 3; ADGRE2 – Adhesion G Protein-Coupled Receptor E2; AdipoR1 – Adiponectin Receptor 1; AT1R – Angiotensin II Type 1 Receptor; GPR180 – G protein Coupled Receptor 180; 7TM – seven trans-membrane.

linked GPR180 variants to metabolic traits such as plasma triglyceride (TAG) levels (Etheridge et al. 2020) and liver lipid regulation (Pandey et al. 2024). The GPR180 locus was identified in large-scale meta-analyses as associated with elevated circulating TAG in populations, highlighting its role in dyslipidaemia. Notably, recent human genetic and single-cell transcriptomic studies have further associated GPR180 with genetic variants that contribute to the risk of adverse cardiometabolic outcomes. This reinforces its significance in metabolic tissues (Kar et al. 2026). Beyond metabolic phenotypes, GPR180 variants have also been linked to diverse traits, including congenital microcoria, fatigue, and tendon injury (Pozza et al. 2020; Kim et al. 2021; Kobayashi et al. 2025), underscoring their broader physiological relevance. Collectively, these observations position GPR180 as a valuable model for exploring how proteins originally classified as GPCRs can engage non-canonical signalling pathways to integrate extracellular cues with organelle function and tissue-specific metabolic regulation.

Molecular insights into GPR180 and its non-canonical signalling

GPR180 was initially annotated as an orphan GPCR based on its predicted 7TM structure – a feature historically used for classification – and designated as the intimal thickness receptor (ITR), with weak rhodopsin-like (Class A) motifs (Tsukada et al. 2003). At the primary sequence level, however, it shows little homology to characterized GPCRs. While transmembrane segments share partial motif similarity with the rhodopsin-like superfamily, structural predictions alone are insufficient for functional GPCR designation. Current practice requires direct evidence of heterotrimeric G-protein coupling and downstream second-messenger activation (e.g., cAMP or Ca²⁺ signalling) for classification as a GPCR (Zhang et al. 2024). To date, no study has provided direct evidence that GPR180 couples to defined G α subunits or elicits classical second-messenger responses, despite multiple attempts to characterize its signalling properties in heterologous expression systems (Balazova et al. 2021; Yoshida et al. 2023; Mitrovic et al. 2024). Some reports have suggested indirect links between GPR180 and Gi-dependent or PKG-associated signalling pathways, particularly in vascular contexts (Wang et al. 2022; Zhang et al. 2023). However, these studies do not establish direct receptor-G protein coupling and often rely primarily on downstream pharmacological inference rather

than proximal signalling assays. Taken together, the available evidence does not support the current classification of GPR180 as a *bona fide* G protein-coupled receptor and instead points toward alternative signalling mechanisms.

Instead, GPR180 aligns conceptually with a growing group of 7TM proteins that lack canonical GPCR signalling despite sharing elements of GPCR-like structural architecture. A well-established precedent for this distinction is provided by adiponectin receptors (AdipoR1 and AdipoR2), which also possess a 7TM architecture but exhibit reverse topology relative to classical GPCRs. Adiponectin receptors thus signal independently of heterotrimeric G proteins, most prominently through AMPK-dependent pathways (Yamauchi et al. 2003). Importantly, our previous study demonstrated that GPR180 similarly displays inverted membrane orientation, despite its GPCR-like annotation based on predicted transmembrane structure (Balazova et al. 2021). Together, these observations illustrate how a 7TM architecture can accommodate alternative signalling paradigms and underscore that receptor classification must be grounded in experimentally validated signalling mechanisms rather than structural prediction alone, consistent with the broader hallmarks of atypical receptor signalling outlined in Box 1.

Notably, despite its limited homology to established GPCR families, GPR180 is highly conserved across mammalian species. Human and mouse GPR180 share ~75% amino acid identity, with similarly high conservation observed between human and rat orthologs (~80% identity, depending on alignment parameters) in UniProt and NCBI sequence databases. This degree of evolutionary conservation argues against GPR180 being a rapidly diverging or lineage-specific protein. Instead, it suggests that key structural features – including the 7TM helices and intervening intra- and extracellular loops – are under strong evolutionary constraint. Such conservation supports the relevance of rodent models for functional studies. It also implies that non-canonical functions attributed to GPR180 are likely preserved across species and physiologically meaningful rather than artifacts of particular model systems.

In addition to transmembrane helices, GPR180 contains a GOLD (Golgi dynamics) domain (Mitrovic et al. 2024), a β -sandwich fold originally characterized in proteins involved in membrane trafficking and organelle organization (Anantharaman and Aravind 2002). The GOLD domain is thought to mediate protein-protein interactions and has been implicated

in regulating trafficking between the endoplasmic reticulum (ER), Golgi, and endosomal compartments. Such domains are not a feature of canonical GPCRs and instead point to roles in scaffolding or the assembly of membrane-associated complexes. In the case of GPR180, the presence of a GOLD domain suggests a potential connection to intracellular membrane trafficking and compartmental organization. Consistent with this, functional studies have shown that perturbation of GPR180 affects mitochondrial metabolic activity and energy metabolism in adipocytes (Balazova *et al.* 2021). While the precise interactome of the GPR180 GOLD domain remains incompletely defined, its presence distinguishes the protein from canonical GPCRs. It also highlights its potential role in organizing membrane-associated protein complexes and signalling platforms linking secretory and metabolic compartments.

Subcellular localization studies further highlight GPR180's atypical nature. In differentiated adipocytes, GPR180 is detected at the plasma membrane, as shown by receptor staining in non-permeabilized cells (Balazova *et al.* 2021). Independent work in other cellular systems has revealed that GPR180 can also localize to intracellular vesicular structures, which are likely acidic compartments, indicating dynamic receptor trafficking and exposure to multiple membrane environments (Mitrovic *et al.* 2024). These observations suggest that GPR180 is not restricted to the plasma membrane, consistent with the spatially compartmentalized signalling highlighted in Box 1. Collectively, these data suggest that GPR180 can operate in multiple membrane compartments, potentially enabling localized regulation of intracellular complexes and metabolic processes.

At the signalling level, emerging evidence links GPR180 to multiple regulatory pathways involved in metabolic control. One such connection involves the TGF β signalling cascade (Balazova *et al.* 2021). Knockdown or genetic deletion of GPR180 in adipocytes blunts TGF β 1-induced SMAD2/3 phosphorylation and downstream transcriptional responses, phenocopying perturbations in canonical TGF β receptor signalling, while GPR180 overexpression induces SMAD3 phosphorylation, further supporting a modulatory role in TGF β receptor complexes (Balazova *et al.* 2021). In addition, Yoshida *et al.* (2023) identified GPR180 as a regulator of hepatic mTORC1 signalling, where loss of GPR180 reduced mTORC1 activity and altered metabolic gene programs in the liver. Together, these observations suggest that GPR180 may participate in multiple signalling contexts that

converge on the control of cellular metabolism. Other interaction partners remain incompletely defined, and unbiased interactomics approaches would be valuable to elucidate the GPR180-associated signalling network. To date, no high-confidence direct interactions with heterotrimeric G proteins or canonical GPCR effectors (G α_s , G α_q , G α_i/o) have been reported. Thus, the absence of canonical G protein outputs, together with its apparent role in modulating TGF β –SMAD signalling complexes and mTORC1 signalling pathways, places GPR180 closer to a contextual signalling scaffold than to a traditional GPCR. Rather than operating through classical GPCR signalling cascades, GPR180 appears to influence cellular metabolic programs through atypical, context-dependent mechanisms. In this regard, GPR180 illustrates how 7TM proteins can engage non-canonical signalling strategies that are physiologically meaningful despite deviating from textbook GPCR paradigms, consistent with the broader functional features outlined in Box 1.

Energy metabolism as a core output of GPR180 function

Across metabolic tissues examined to date, alterations in cellular energy metabolism represent a recurring functional consequence of GPR180 perturbation. In adipocytes, manipulation of GPR180 expression alters mitochondrial metabolic activity and cellular bioenergetics, including oxidative metabolism and ATP availability (Balazova *et al.* 2021). In the liver, GPR180 has been linked to the regulation of mTORC1 signalling, a central metabolic hub, and metabolic gene programs, further supporting its role in controlling metabolic pathways (Yoshida *et al.* 2023). Rather than eliciting rapid second-messenger responses characteristic of canonical GPCR signalling, these observations suggest that GPR180 primarily influences cellular metabolic outputs. Importantly, the consequences of GPR180 perturbation appear to be tissue-dependent, consistent with the distinct energetic demands and functional specializations of metabolic organs such as adipose tissue and liver (Balazova *et al.* 2021; Yoshida *et al.* 2023; Zhang *et al.* 2023; Zhu *et al.* 2025). In the following sections, we summarize current evidence supporting a role of GPR180 in metabolic regulation and discuss how its function manifests in a context-specific manner across tissues (Figure 2).

Control of adipocyte energy metabolism by GPR180. Adipose tissue studies provide the most comprehensive functional evidence linking GPR180

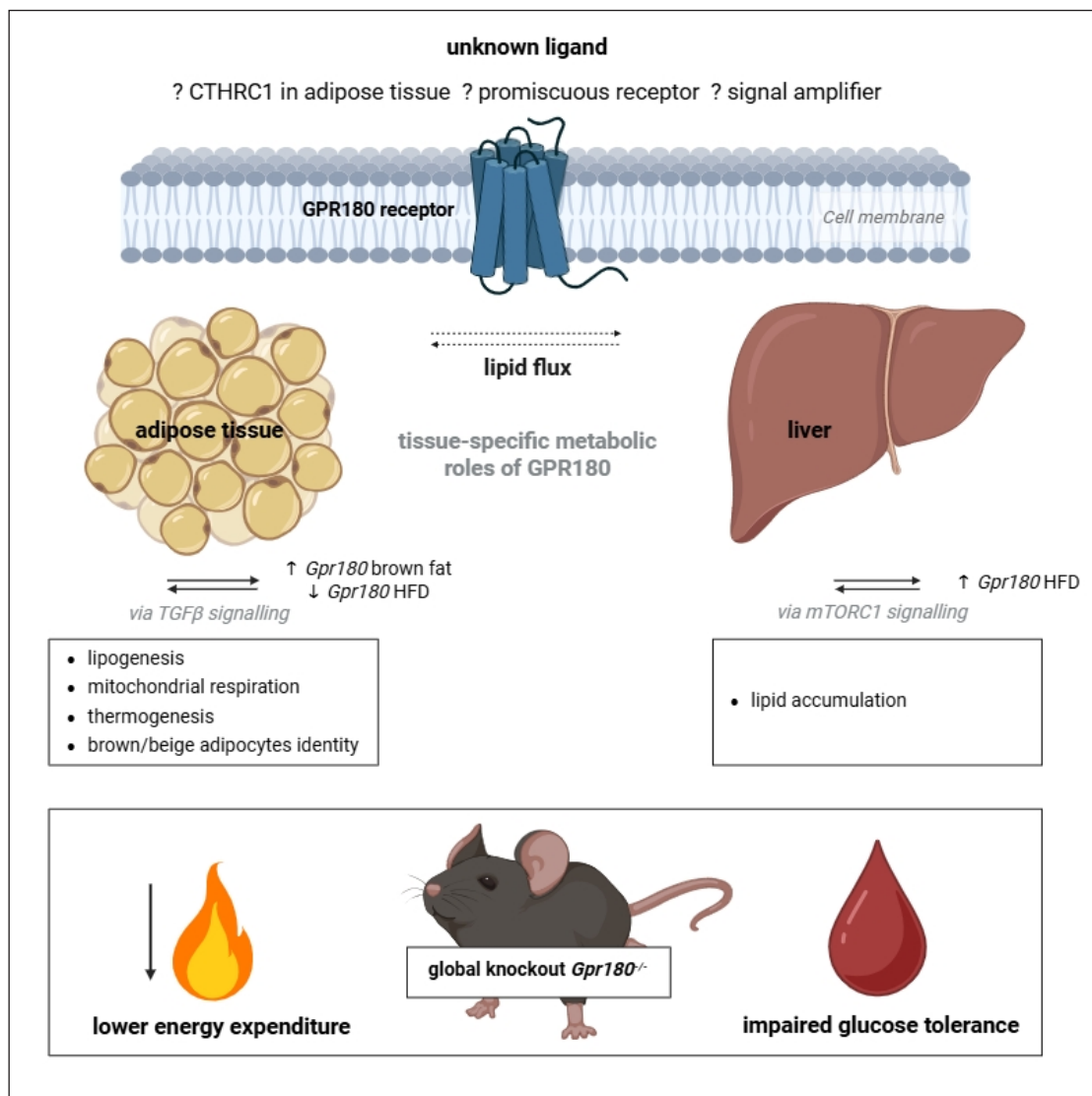


Figure 2. Conceptual model of tissue-specific metabolic functions of GPR180. GPR180 is a seven-transmembrane protein with currently unknown endogenous ligand(s). Several possible modulatory mechanisms have been proposed, including interactions with extracellular factors such as CTHRC1, receptor promiscuity, or signal amplification. In adipose tissue, GPR180 regulates key metabolic processes through TGFβ-associated signalling pathways. Functional studies indicate that GPR180 influences adipocyte lipid metabolism, mitochondrial respiration, thermogenic capacity, and the maintenance of brown and beige adipocyte identity. In the liver, emerging evidence suggests that GPR180 modulates hepatic lipid metabolism through mechanisms linked to mTORC1 signalling, influencing hepatic lipid accumulation. At the organismal level, global *Gpr180* knockout mice display systemic metabolic alterations, including reduced energy expenditure and impaired glucose tolerance, indicating that GPR180 contributes to whole-body metabolic homeostasis. Together, these findings highlight tissue-specific roles of GPR180 in metabolic regulation and illustrate how atypical seven-transmembrane proteins can influence systemic energy balance through distinct signalling mechanisms in different metabolic organs. Abbreviations: CTHRC1 – Collagen triple helix repeat containing 1; GPR180 – G protein Coupled Receptor 180; mTORC1 – Mammalian target of rapamycin complex 1; TGFβ – Transforming growth factor β.

to cellular energy metabolism. GPR180 expression is dynamically regulated in adipose tissue, with levels varying across fat depots and developmental stages. It is higher in visceral fat depot than in subcutaneous

adipose tissue and is enriched in differentiated adipocytes compared to preadipocytes. In addition, *Gpr180* expression in white adipose tissue decreases upon high-fat diet feeding, indicating sensitivity to

metabolic stress. Moreover, *GPR180* is upregulated in thermogenic brown fat on both the cellular and tissue levels (Balazova et al. 2021; Zhu et al. 2025).

Functional studies indicate that GPR180 is important for adipocyte metabolic capacity. *In vitro*, loss of *GPR180* in human brown adipocytes reduces UCP1 expression and uncoupled mitochondrial respiration, thereby suppressing the brown phenotype. In contrast, *GPR180* overexpression in human white adipocytes induces UCP1 and increases uncoupled respiration along with enhanced respiratory capacity, promoting a browning-like program (Balazova et al. 2021). Mechanistically, these data suggest that GPR180-dependent modulation of mitochondrial bioenergetics underlies the changes in adipocyte identity.

Complementing these *in vitro* studies, global *Gpr180* knockout mice display reduced UCP1 expression in both brown and subcutaneous white adipose tissues, reflecting impaired thermogenic capacity. These mice also exhibit lower energy expenditure, reduced maintenance of body temperature, and metabolic dysfunction, including impaired glucose tolerance and accelerated body weight gain on a high-fat diet. Adipocyte-specific *Gpr180* deletion largely recapitulates these effects, underscoring an adipocyte-autonomous mechanism with whole-body consequences (Balazova et al. 2021). The study of Zhu et al. (2025) supports a broader role for GPR180 in adipocyte metabolic function. It demonstrates that *in vivo* *Gpr180* overexpression in subcutaneous fat improves glucose tolerance and insulin sensitivity. It also diminishes weight gain induced by a high-fat diet, accompanied by a reduction in adipose tissue characterized by smaller adipocytes. This effect is attributed to the suppression of lipogenesis and the inhibition of fatty acid uptake. These findings suggest that GPR180 plays a role in lipid storage control (Zhu et al. 2025).

Importantly, recent single-cell omics analyses of human subcutaneous adipose tissue further implicate GPR180 in metabolic regulation at the population level. A cis-eQTL regulating adipocyte GPR180 expression colocalizes with triglyceride GWAS signals, with the risk allele enriched in individuals of Mexican ancestry, thereby establishing a connection between GPR180 and ancestry-stratified variants that contribute to the risk of adverse cardiometabolic outcomes (Kar et al. 2026). These findings expand upon experimental observations by situating GPR180 within human adipose gene regulatory networks related to lipid metabolism and offer genetic evidence supporting its role in adipocyte function.

Together, these findings illustrate that GPR180 facilitates adaptive thermogenesis and lipid homeostasis by linking mitochondrial substrate oxidation to UCP1-dependent thermogenic heat production in brown and beige adipocytes, thus maintaining the thermogenic identity of these cells. By promoting energy dissipation rather than ATP synthesis, GPR180 supports metabolic flexibility across various adipose tissues, thereby modulating both thermogenic potential and lipid metabolism efficiency.

Emerging role of GPR180 in hepatic metabolism.

GPR180 is expressed in the liver, wherein its expression increases under obesogenic conditions and lipid overload (Zhang et al. 2023). Human genetic studies further implicate GPR180 in hepatic lipid metabolism, with variants at the GPR180 locus being associated with liver fat content and related metabolic traits (Pandey et al. 2024). In addition, functional studies consistently recognize GPR180 as a modulator of hepatic lipid handling, although reported outcomes vary by experimental design and tissue context.

Global *Gpr180* knockout models have demonstrated seemingly contradictory hepatic phenotypes. In the study by Balazova et al. (2021), whole-body deletion exacerbated hepatic steatosis. Conversely, Yoshida et al. (2023) reported that global *Gpr180* deficiency alleviated diet-induced lipid accumulation, which was associated with reduced mTORC1 signalling and suppression of lipogenic pathways. Notably, ablation of *Gpr180* specifically in hepatocytes results in a more consistent phenotype. Targeted deletion of *Gpr180* in hepatocytes diminishes hepatic triglyceride accumulation and enhances metabolic parameters during high-fat feeding, including glucose tolerance and insulin sensitivity (Yoshida et al. 2023; Zhang et al. 2023). Conversely, hepatic overexpression of *Gpr180* promotes lipid accumulation. This finding underscores a cell-intrinsic role for GPR180 in facilitating hepatocellular lipid storage pathways.

The resolution of discrepancies in global knockout studies may reside in inter-organ crosstalk. In the context of comprehensive systemic deletion, impairments in adipose tissue thermogenesis and alterations in lipid mobilization could lead to a redirection of excess fatty acids to the liver, thereby intensifying steatosis (Balazova et al. 2021). Conversely, intrinsic suppression of lipid deposition pathways within hepatocytes, as described by Yoshida et al. (2023), may offer protective effects when systemic lipid flux is not predominant. Supporting this inter-organ communication model,

adipose-specific overexpression of *Gpr180* has been shown to reduce hepatic lipid accumulation and decrease hepatocyte lipid droplet size, suggesting a tendency toward improved lipid partitioning toward thermogenic adipose tissue (Zhu et al. 2025).

Taken together, these findings support a model in which GPR180 exerts bidirectional control over hepatic lipid metabolism: it promotes lipid deposition through hepatocyte-autonomous mechanisms, while its activity in adipose tissue favours lipid utilization and thermogenesis. The net hepatic phenotype, therefore, depends on tissue predominance and metabolic context. Rather than exerting a uniform effect on steatosis, GPR180 appears to modulate hepatic metabolic flexibility through coordinated inter-organ regulation of lipid flux.

Expanding metabolic functions of GPR180 across tissues. GPR180 is also expressed in other metabolically active tissues, including skeletal muscle and pancreatic islets (Tsukada et al. 2003), suggesting that its metabolic functions may extend beyond adipose tissue and liver. Emerging evidence further indicates that GPR180 may influence pancreatic β -cell function and glucose-stimulated insulin secretion (GSIS) (Antal et al. 2026), suggesting a potential role in endocrine control of glucose homeostasis. Together, these observations suggest that GPR180-dependent regulation of cellular metabolism may operate across multiple metabolic organs, although the underlying mechanisms remain to be defined.

Open questions and future direction

Despite growing evidence that GPR180 plays a key role in regulating energy metabolism, several fundamental questions remain unresolved. Addressing these gaps will be essential to fully understand how this atypical 7TM protein contributes to metabolic homeostasis and disease.

What activates GPR180? To date, no endogenous ligand has been conclusively identified for GPR180, and it remains classified as an orphan receptor. Classical GPCR ligand paradigms may not apply, consistent with its atypical signalling behaviour and lack of demonstrated G-protein coupling. Our study of adipose tissue identified the secreted protein Collagen triple helix repeat containing 1 (CTHRC1) as an extracellular signal that requires GPR180 to regulate adipocyte metabolic programs (Balazova et al. 2021). While these findings provide an important starting point, direct binding, tissue specificity, and the molecular basis of this interaction remain to be determined.

In addition to CTHRC1, heterologous expression studies have suggested that certain metabolites may interact with GPR180. For example, unbiased receptor screens in neuronal cell systems identified GPR180 as a candidate lactate-sensitive orphan receptor, with L-lactate modulating intracellular cyclic AMP responses through GPR180 in a heterologous expression context (Mosienko et al. 2018). However, these observations have not been validated in metabolic tissues or confirmed at physiologically relevant lactate concentrations *in vivo*, and the putative lactate–GPR180 interaction remains to be rigorously tested with direct binding and functional assays. Therefore, while intriguing, lactate cannot yet be considered a validated endogenous activator of GPR180 in metabolic regulation.

Apart from these two candidates, the literature has not convincingly validated any additional ligands – whether protein, peptide, or small-molecule. This highlights the necessity for systematic approaches to ligand discovery. Consequently, alternative modes of activation should be considered. These may encompass ligand-independent scaffolding functions, regulation through receptor trafficking or subcellular localization, and conformational modulation by environmental factors such as pH, in line with recent structural and biophysical findings. Such mechanisms would reposition GPR180 closer to a metabolic sensor or signalling hub rather than a traditional ligand-gated receptor.

How does cellular context shape GPR180 function? Another major open question concerns the strong context-dependent phenotypes of GPR180 across tissues and experimental models. Divergent outcomes in adipose tissue and liver, along with differences between global and tissue-specific manipulations, suggest that GPR180 does not operate through a single linear pathway. Instead, its functional output likely depends on cell type, metabolic state, developmental timing, and the availability of interacting partners. Resolving how these variables shape GPR180 signalling will be critical for reconciling seemingly opposing phenotypes and for understanding its role in inter-organ metabolic crosstalk.

What are the proximal signalling mechanisms? At the mechanistic level, the immediate molecular partners and signalling complexes associated with GPR180 remain poorly defined. Although links to TGF β pathway components have been established, and recent studies also implicate GPR180 in the modulation of mTORC1 signalling, it remains unclear whether GPR180 acts as a scaffold, a

trafficking regulator, or a modulator of receptor complex assembly. The presence of a GOLD domain and evidence for intracellular vesicular localization suggest roles in the assembly of membrane-associated signalling complexes rather than in the direct engagement of classical GPCR effectors. Future work will be required to determine whether GPR180 coordinates multiple signalling modules, including TGF β -related pathways and nutrient-sensing regulators such as mTORC1. Unbiased interactomics and spatially resolved proteomic approaches will be essential to clarify these proximal mechanisms.

Emerging structural classification and metabolic specialization. Recent evolutionary and structural analyses reclassify GPR180 within a conserved GOST protein family (GOLD domain 7TM helix proteins), alongside GPR107, GPR108, TMEM145, and Wntless, across holozoan species (Mitrovic *et al.* 2024; Garcia De Las Bayonas and King 2025). These studies emphasize the shared GOLD + 7TM architecture and intracellular localization of GOST proteins, while noting the lack of clear evidence for canonical heterotrimeric G-protein coupling (Figure 1C). Importantly, this work provides a structural and evolutionary framework for understanding why GPR180 was historically annotated as a GPCR, but it does not address tissue-specific metabolic functions.

Within this family, Wntless (WLS/GPR177) is best characterized as a secretion chaperone for lipidated Wnt signalling proteins rather than as a mediator of receptor-mediated signal transduction (Banziger *et al.* 2006). WLS appears to be required for pancreatic development (Carpenter *et al.* 2010), metabolic zonation programs in the liver (Ma *et al.* 2020), and adipose tissue lipogenesis (Bagchi *et al.* 2020). Furthermore, its consistent downregulation across various brown adipose tissue depots compared with adjacent white adipose tissue, as well as in brown hMADS-derived adipocytes (Perdikari *et al.* 2018; Wu *et al.* 2025), suggests a potential role in regulating the thermogenic program. These findings indicate that WLS-dependent Wnt trafficking contributes to metabolic tissue plasticity and systemic metabolic homeostasis.

GPR107 and GPR108 have been localized to the Golgi network and linked to retrograde transport or antiviral immunity (Tafesse *et al.* 2014; Zhao *et al.* 2023). Both proteins are widely expressed across human tissues, including adipose tissue, liver, skeletal muscle and pancreas, as documented by the Human Protein Atlas. However, their specific metabolic functions within these organs remain to be definitively characterized. To date, none of these

proteins has been shown to function as a canonical GPCR.

Structurally related GOLD-domain 7TM proteins, including TMEM87A and TMEM87B (often classified within the LUSTR family), contain predicted 7TM segments together with luminal GOLD-like domains (Edgar 2007; Hoel *et al.* 2022). Although not always formally grouped within the core GOST designation, their domain organization and overall architecture support the existence of a broader GOLD-7TM protein superfamily. Members of this group have primarily been linked to membrane trafficking and organelle-associated processes rather than classical receptor-mediated signal transduction. To date, clear metabolic functions for TMEM87A or TMEM87B in the liver, adipose tissue, or pancreas have not been established, despite their widespread expression across human tissues as reported by the Human Protein Atlas.

TMEM145, a putative paralogue of GPR180 based on sequence similarity and predicted structural features, has also been assigned to the broader GOST protein family. Nevertheless, its physiological function remains largely undefined, and its potential contribution to metabolic regulation has yet to be established.

We propose that GPR180 represents a prototypical member of a metabolically specialized GOST subclass, defined by:

- **Inverted 7TM topology** (distinct from canonical GPCR architecture)
- **Control of cellular metabolic capacity and organelle function**
- **Shaping of metabolic cell phenotypes** (thermogenesis and lipid handling)
- **Tissue-specific physiological impact** (with the strongest current evidence in adipose tissue and liver)

Unlike other GOST family members, which have primarily been studied in the context of membrane trafficking, GPR180 consistently modulates core metabolic phenotypes across multiple tissues. This positions it as a defining member of a metabolically specialized subset within the GOST family, characterized by modulation of tissue-specific metabolic phenotypes rather than classical GPCR signalling. Recognizing this subclass provides a conceptual framework for identifying additional 7TM proteins whose physiological functions cannot be predicted solely from GPCR-like architecture.

Broader implications. More broadly, GPR180 challenges traditional frameworks for classifying 7TM proteins. Its effects on mitochondrial function, lipid handling, and long-term metabolic cell identity—without canonical G protein signalling—highlight the need to expand receptor biology beyond second-messenger paradigms. Understanding GPR180 may therefore provide insights not only into metabolic regulation, but also into a broader class of atypical 7TM proteins whose functions remain under-explored. Systematic screening of GOST family members for metabolic phenotypes is needed to test whether additional regulators of tissue-specific energy homeostasis await discovery within this emerging subclass.

Conclusion

Collectively, the evidence reviewed here demonstrates that GPR180 has been misannotated as a classical G protein-coupled receptor, primarily based on predicted 7TM structure rather than experimentally validated signalling mechanisms. Although GPR180 exhibits a GPCR-like structural architecture, its inverted membrane topology and lack of demonstrable coupling to heterotrimeric G proteins clearly distinguish it from *bona fide* GPCRs. Instead, GPR180 operates through atypical mechanisms that influence metabolic capacity and long-term cell

identity. Findings across metabolic tissues suggest that its functional output is shaped by cellular context and metabolic state and point to potential roles for subcellular organization and protein interactions that remain to be directly tested. Re-appraising GPR180, therefore, not only refines our understanding of its role in metabolic regulation, but also underscores broader challenges in annotating orphan 7TM proteins whose functions extend beyond classical signalling paradigms. We anticipate that similar re-appraisals of other structurally defined ‘orphan GPCRs’ in metabolically active tissues will reveal additional 7TM receptors whose primary outputs are tissue-specific metabolic control rather than canonical G protein signalling.

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