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# G protein-coupled receptor 146: new insights from genetics and model systems

Umesh Tharehalli<sup>a</sup> and Antoine Rimbert<sup>b</sup>

## Purpose of review

Atherosclerotic cardiovascular diseases continue to be a significant global cause of death. Despite the availability of efficient treatments, there is an ongoing need for innovative strategies to lower lipid levels, especially for individuals experiencing refractory dyslipidemias or intolerable adverse effects. Based on human genetic findings and on mouse studies, the G protein-coupled receptor 146 (GPR146) emerges as a promising target against hypercholesterolemia and atherosclerosis. The present review aims at providing a thorough summary of the latest information acquired regarding GPR146, encompassing genetic evidence, functional insights, and its broader implications for cardiometabolic health.

## Recent findings

Human genetic studies uncovered associations between GPR146 variants, plasma lipid levels and metabolic parameters. Additionally, GPR146's influence extends beyond lipid regulation, impacting adipocyte differentiation, lipolysis, and inflammation pathways. Despite GPR146's orphan status, ongoing efforts to deorphanize it, suggest a potential ligand with downstream effects involving Gαi coupling.

## Summary

Here, we outline and deliberate on recent progress focused on: enhancing comprehension of the effects of inhibiting GPR146 in humans through genetic instruments, evaluating the extra-hepatic functions of GPR146, and discovering its natural ligand(s). Grasping these biological parameters and mechanisms is crucial in the exploration of GPR146 as a prospective therapeutic target.

## Keywords

cardiometabolic diseases, deorphanization, extra-hepatic action, G protein-coupled receptor 146, signaling pathway

## INTRODUCTION

Despite a significant reduction in recent decades, atherosclerotic cardiovascular diseases (ASCVD) continue to be the foremost global cause of death [1,2]. Elevated levels of low-density lipoprotein cholesterol (LDL-C) in the bloodstream remain the primary risk factor and the primary focus for managing ASCVD [3]. Although effective medications are available, and recent additions have broadened therapeutic options, there is a demand for innovative lipid-lowering treatments to further decrease the risk of ASCVD. Specifically, there is a need for alternatives for individuals with: severe dyslipidemias that do not respond to existing treatments, those experiencing intolerable or harmful adverse effects from current therapies, or individuals with residual ASCVD risk despite apparently acceptable responses to the current standard of care. Additionally, the prevalence of metabolic syndrome, characterized by visceral obesity, insulin resistance, and type 2 diabetes, is consistently increasing, leading to ASCVD

patients presenting with growing metabolic comorbidities like type 2 diabetes and liver steatosis.

Recently, the G protein-coupled receptor 146 (GPR146), a member of the G-coupled protein receptors' family widely utilized in pharmaceutical targeting, has been identified as a regulator of plasma cholesterol levels [4,5]. In mice, the inhibition of GPR146 in the liver exhibits promising characteristics, providing protective effects against hypercholesterolemia and atherosclerosis [4]. Significantly, unlike statins and PCSK9 inhibitors, the mechanism

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## KEY POINTS

- Genetic studies showed that a lower G protein-coupled receptor 146 (GPR146) gene-expression is associated with reduced risk of dyslipidemia and cardiovascular diseases and a favorable profile of metabolic circulating markers.
- GPR146's role in adipose tissue: Despite being highly expressed in adipose tissue, the precise function of GPR146 in adipose tissue remains unclear. Knockdown experiments in 3T3-L1 preadipocytes suggest that GPR146 downregulation compromises adipogenic differentiation and leads to increased lipolysis, indicating a potential regulatory role in adipocyte biology.
- GPR146's impact on endothelial inflammation: GPR146 expression in endothelial cells appears to modulate inflammation independently of Gs/Gαs and cyclic adenosine monophosphate (cAMP) pathways. Knockdown of GPR146 leads to increased p65 phosphorylation, suggesting its possible involvement in regulating inflammation pathways in response to disturbed blood flow. However, the exact mechanism by which GPR146 influences endothelial inflammation and its potential role in lipid channeling at the endothelial cell barrier remain to be fully elucidated.

of GPR146 signaling on cholesterol homeostasis operates independently of the LDL receptor pathway, making it particularly relevant for patients with homozygous familial hypercholesterolemia. Considering that GPRs are prime druggable targets, these findings nourished hope for the identification of GPR146 ligand(s) and the development of small molecules to inhibit GPR146 and to improve the management of hypercholesterolemia, including HoFH and ASCVD [6–8]. In this document, our main objective is to present a comprehensive overview of genetic evidence establishing connections between genetic variations impacting GPR146 function and phenotypes observed in both the general population and familial cases. Furthermore, we seek to delineate recent discoveries regarding the biological mechanisms associated with GPR146, and to explore its wider implications on cardiometabolic health, utilizing diverse models for a more thorough understanding.

## GENETIC EVIDENCES AND ASSOCIATED PHENOTYPES

### Identification of common variants associated with plasma lipid levels

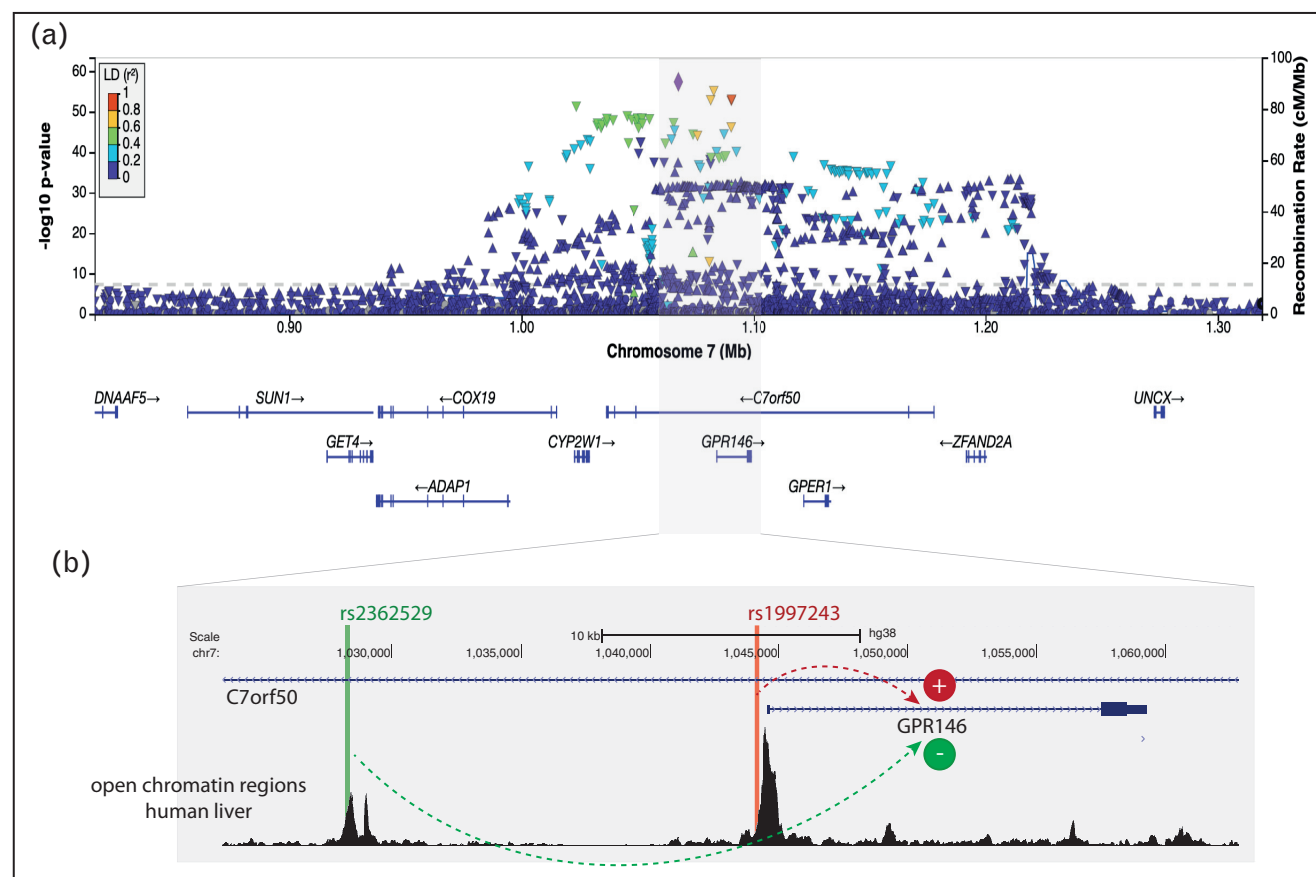
In 2013, Willer *et al.* [9] initially reported the first genetic association between genetic variants in the *GPR146* locus and plasma lipids. Specifically, the

study revealed a significant association between the rs1997243 (G-allele) and elevated levels of plasma cholesterol. Subsequent investigations have consistently confirmed this association, extending it to, not only increased plasma cholesterol, but also elevated levels of HDL-C [10] and LDL-C [11]. The continuous advancements in genotyping chips and the improvement of imputation panels have led to a more precise delineation of associated *loci*. As a result, the identification of rs2362529 (C-allele) has emerged as another significant association, demonstrating lowered plasma levels of total cholesterol, LDL-C, non-HDL-C, and HDL-C across various populations [11–13] (Fig. 1a). Crucially, the two aforementioned common variants, rs1997243 and rs2362529, are not in linkage disequilibrium [14<sup>\*</sup>], indicating their status as independent genetic associations.

### Locus refinement

Rs1997243 and rs2362529 are situated in noncoding regions, introducing uncertainty in identifying the causal gene within the *locus*. To refine this genetic locus, several studies have sought evidence supporting the involvement of *GPR146* as the causal gene and these variants as causal ones. Initially, the rs1997243 variant exhibits strong linkage disequilibrium with a coding variant in *GPR146* (*GPR146* p.Gly11Glu, Fig. 2). Although this supports a role for *GPR146*, the *GPR146* p.Gly11 residue lacks conservation, being substituted with Asp, Asn, or Ala in many other species. Furthermore, bioinformatics prediction tools classify *GPR146* p.Gly11Glu as benign or neutral [4,5]. These observations make it less likely that the variant *GPR146* p.Gly11Glu is the disease-causing variant. However, experimental data are lacking to assess the functionality of *GPR146* p.Gly11Glu, located in the N-terminal extracellular domain of GR146 (Fig. 2).

Subsequent to these observations, various groups tested the hypothesis that the rs1997243 variant might influence the expression of nearby genes in the locus. *In silico* analysis revealed that rs1997243 is located in a region enriched with the promoter-specific histone marker H3K4me3 in the liver [5] and is linked to increased expression of *GPR146* in whole blood [4,5]. Han *et al.*, utilizing *in vitro* systems, demonstrated that targeted activation of the rs1997243 site significantly increased *GPR146* expression, with no detectable change in other genes in the locus. They further illustrated that rs1997243 exhibited enhanced promoter activity compared to its reference allele using reporter systems. In contrast to the findings for rs1997243, a recent study revealed that rs2362529 is associated



**FIGURE 1.** Regional plot of the GPR146 locus (7p22). (a) Association results for SNPs ( $-\log_{10} P$  value, y-axis) as a function of genomic coordinates using human gene version 19 (hg19) for GPR146 with plasma total cholesterol (data from Graham *et al.* [12]). The bottom panel shows genes in the locus, as annotated in the UCSC Genome Browser. The top associated SNP (rs2362529) is represented as a purple diamond and the linkage disequilibrium (LD) values (1000 Genomes data) are in the inset. Light blue lines indicate estimated recombination hotspots. (b) Liver open chromatin regions assessed by ATAC-Sequencing [16] and colocalization with top SNPs associated with plasma cholesterol levels. rs2362529 (green) and rs1997243 (red) are located in open chromatin regions and have been found associated with decreased and increased GPR146 gene expression (using expression quantitative trait loci data).

with a reduction in *GPR146* expression [14]. Notably, both cited variants are located in open-chromatin regions in the liver (*this review*, data from [15]), providing additional support for their impact on the gene expression of *GPR146* (Fig. 1b).

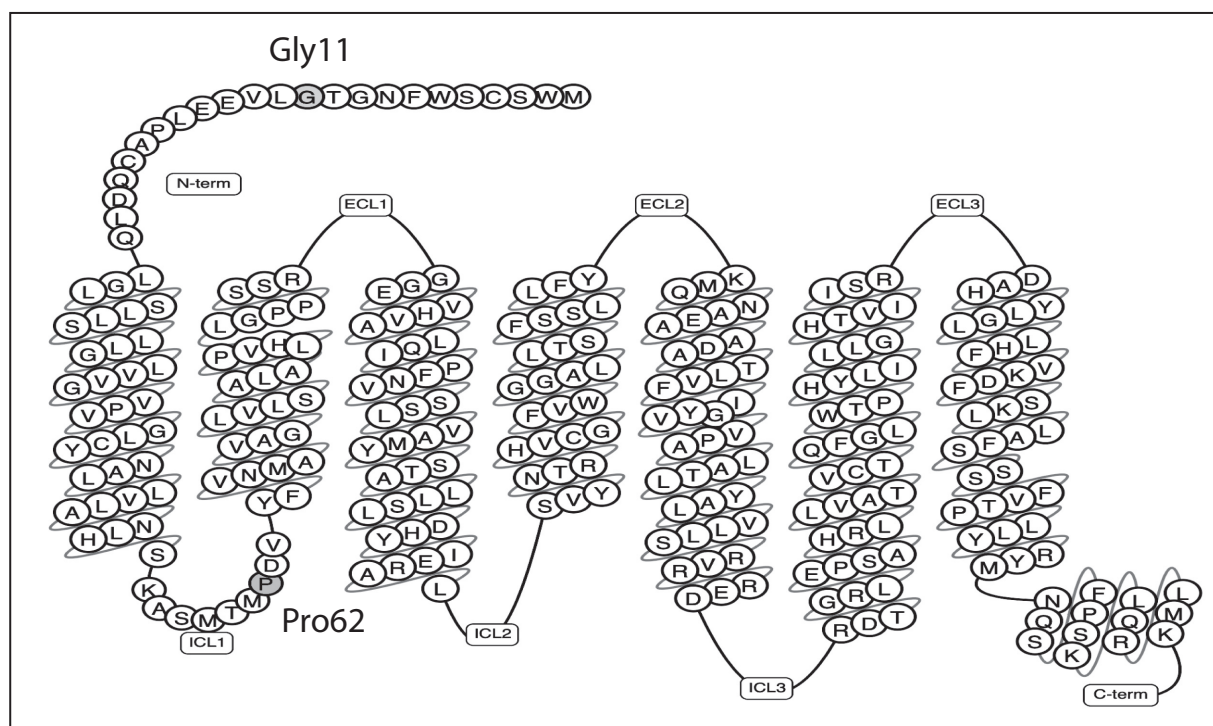
### Co-associations

Rs1997243 and rs2362529, linked respectively to heightened and diminished expression of *GPR146*, can be considered independent genetic tools for investigating phenotypic associations related to the genetic 'activation' or 'inhibition' of *GPR146*. Employing this methodology across a wide range of phenotypes from the UK Biobank, we initially confirmed the initial observation that 'genetic inhibition' of *GPR146* (utilizing rs2362529 as an instrument) is significantly associated with plasma

total cholesterol, LDL-C, and HDL-C, without impacting triglycerides or lipoprotein(a) plasma levels [14]. Additionally, utilizing data from the CARDIoGRAMplusC4D Consortium, we found that carriers of the rs2362529-C allele exhibit a slight but significant reduction in coronary artery disease compared to noncarriers. Lastly, we noted that rs2362529 is linked to reduced plasma levels of C-reactive protein, aspartate aminotransferase, gamma GT, alkaline phosphatase, and HbA1C plasma levels.

### Rare variants

In an effort to identify rare variants with substantial impact on plasma lipid levels, we conducted a screening for rare variants associated with dyslipidemia in both population-based cohorts and



**FIGURE 2.** Schematic view of the predicted amino-acid sequence and protein structure of GPR146. The Glycine 11 (extracellular N terminal domain) is colored in grey and the Proline 62 (first intracellular loop) in green.

familial cases of dyslipidemia. Within Danish and Dutch populations, we discovered several rare variants, each accounting for less than 1% of the general population, within *GPR146*. Notably, one of these variants, *GPR146*-p.Pro62Leu, was predominantly linked to significant reductions in total cholesterol and LDL plasma levels.

In the genetic screening of *GPR146* within familial cases of hypobetalipoproteinemia, where mutations in conventional lipid genes were ruled out, a proband was identified as heterozygous for the *GPR146*-p.Pro62Leu variant. A co-segregation analysis involving 6 family members indicated that carriers of *GPR146*-p.Pro62Leu exhibit LDL-C levels below the 5th percentile for their age and sex [14<sup>¶</sup>]. The notable association of the *GPR146*-p.Pro62Leu variant with lower cholesterol levels, its co-segregation in a familial case of hypobetalipoproteinemia, and predictions from *in-silico* tools classifying this variant as deleterious for protein functionality collectively support the notion that this variant may compromise the function of GPR146. However, additional mechanistic insights are required to elucidate the actual consequences of *GPR146*-Pro62Leu.

Compelling evidence from mouse studies indicates that inhibiting GPR146 could be a potentially effective strategy for treating hypercholesterolemia,

particularly in patients with homozygous familial hypercholesterolemia, as well as atherosclerotic cardiovascular diseases [4,5]. The genetic evidence discussed above collectively supports this assertion in humans. While functional experiments and interventional trials are essential to validate these findings, the use of genetic tools suggests that inhibiting GPR146 would not lead to adverse effects on liver function and glycemic control. Additionally, most attention has been taken to the effects of GPR146 inhibition on apolipoprotein-B proatherogenic particles (VLDL and LDL-C) but HDL-C and apolipoprotein A1 are significantly reduced. The identification of mechanisms at play in the regulation of HDL-C (and apoA1) might identify new lipid modulating pathways.

### THE KEY ROLE OF G PROTEIN-COUPLED RECEPTOR 146 IN THE LIVER AND ITS AMBIGUOUS SIGNALING PATHWAY

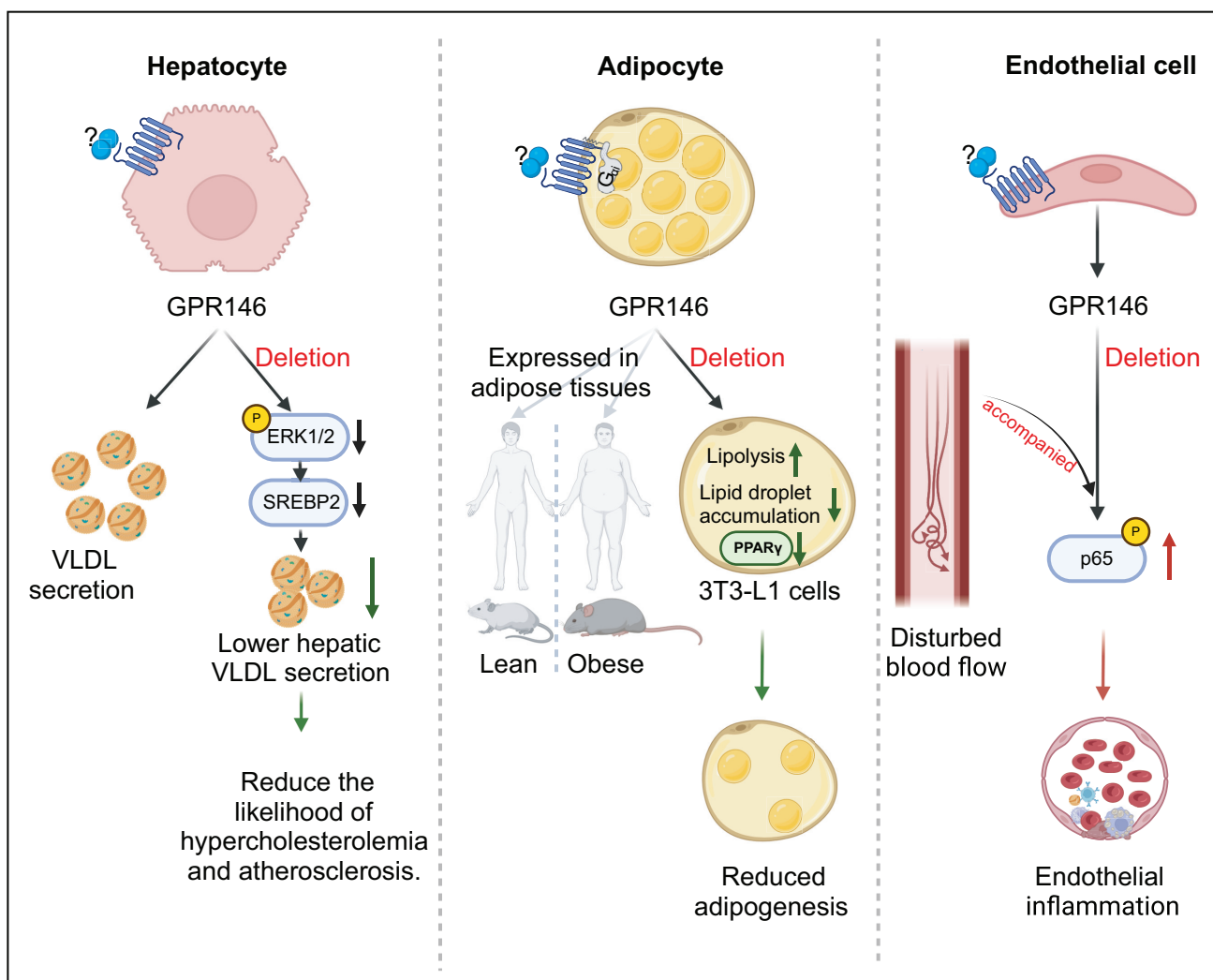
The pivotal function of GPR146 in the liver and its intricate signaling pathway have been extensively explored. The primary functional investigations underscored the significant role of GPR146 in regulating circulating cholesterol concentrations in the liver [4,5], as comprehensively reviewed recently [16<sup>¶</sup>].

In summary, both *in vivo* and *in vitro* studies have demonstrated that the depletion of GPR146 leads to a reduction in the secretion of very low-density lipoproteins (VLDL). Notably, in *Gpr146* knockout mice, no differences were observed in the expression profiles of genes crucial for VLDL secretion, however, there was a significant decrease in transcripts and protein levels of cholesterol homeostasis genes, such as *Hmgcr* and *Srebp2* [4].

Importantly, these effects were noted in mice that were refed after a period of fasting, indicating the dependency of the GPR146-related pathway on

the feeding state. The refed state, mimicked by serum stimulation *in vitro*, was found to induce ERK1/2 phosphorylation through GPR146. Consequently, these findings suggest that the activation of GPR146 is regulated by the feeding axis, and the ensuing intracellular signaling pathway converges on SREBP2 *via* ERK1/2 phosphorylation. This, in turn, regulates the expression of cholesterol biosynthetic genes, ultimately promoting the secretion of VLDL particles from hepatocytes [4] (Fig. 3).

Despite the valuable insights provided by this study into the biological mechanisms at play, the described ERK signaling acts as a molecular hub,



**FIGURE 3.** Schematic representation of GPR146 function in liver, adipocyte, and endothelial cells. (Left panel) In the liver, ablation of *Gpr146* diminishes SREBP2 activity by reducing ERK1/2 phosphorylation, thereby decreasing hepatic secretion of VLDL and lowering circulating cholesterol levels and reduces the risk of atherosclerosis. (Middle panel) Expression of GPR146 is observed in adipocytes from both lean and obese human and mouse models. *In vitro* studies demonstrate that adipocyte-specific loss of *Gpr146* inhibits adipogenesis via PPAR $\gamma$  downregulation, increases lipolysis, and diminishes lipid droplet accumulation. (Right panel) Endothelial cell-specific deletion of *Gpr146* in response to disturbed blood flow triggers NF- $\kappa$ B activation through phosphorylation and nuclear translocation of p65, inducing endothelial inflammation (created with BioRender.com).

raising important questions on the Gpr146-dependency and specificity, and the signaling profile of GPR146 remains ambiguous. In addition to these two primary studies elucidating the crucial role of GPR146 in the liver and offering key insights into the molecular pathways involved, we further delve into recent insights into the extrahepatic function of GPR146.

### SHAPING ADIPOSE TISSUE: G PROTEIN-COUPLED RECEPTOR 146'S ROLE IN THE REGULATION OF ADIPOCYTE DIFFERENTIATION AND LIPOLYSIS

In recent years, there has been a growing interest in exploring whether GPR146 plays a role in lipid metabolism beyond the liver. Based on the tissue-specific mRNA expression, *GPR146* displays significant enrichment in adipose tissue, particularly in humans and mice [4]. However, the adipocyte-specific deletion of *Gpr146* in mice did not affect plasma cholesterol levels [4]. Mahri *et al.* [17] conducted a comprehensive high-throughput RT-qPCR assay to profile nonsensory GPRs in subcutaneous adipose tissues (sAT) from lean, healthy-obese (without diabetes, BMI: 30–49.9 kg/m<sup>2</sup>), and unhealthy obese (with diabetes, BMI: 30–49.9 kg/m<sup>2</sup>) individuals. *GPR146* emerged as one of the most significantly downregulated genes in both groups of obese individuals. Further investigations revealed a significant increased expression of *Gpr146* specifically on day 7 of 3T3-L1 differentiation from preadipocytes into adipocytes [17]. However, the precise role of GPR146 in adipose tissue remains unclear. In alignment with this, Kaczmarek *et al.* [18<sup>¶</sup>] developed the FATTLAS, an interactive web tool, comparing RNA-seq data of adipose tissue from lean and obese humans and mice. Interestingly, *GPR146* exhibited high expression in the sAT of both lean and obese human individuals, and ranking among the top 8% expressed genes in mouse adipose tissue.

To delve deeper into the functional aspects, Kaczmarek *et al.* employed small interfering RNA (siRNA) targeting *Gpr146* in 3T3-L1 preadipocytes. This intervention led to a modest reduction in cellular viability, accompanied by a compromised adipogenic process characterized by the downregulation of the adipogenic marker *Ppar $\gamma$*  [18<sup>¶</sup>] (Fig. 3). Consequently, there was a reduction in the accumulation of lipid droplets. Notably, although the distribution of lipid droplets remained unaltered, both the overall number and individual droplet-size experienced reductions. Collectively, these findings contribute to a nuanced understanding of the attenuated adipogenic differentiation process induced

by *Gpr146* downregulation. Remarkably, this study also demonstrates that knockdown of *Gpr146* results in increased lipolysis, as measured by higher free glycerol in the cell culture supernatant [18<sup>¶</sup>].

### INFLAMMATORY INSIGHTS: G PROTEIN-COUPLED RECEPTOR 146'S IMPACT ON INFLAMMATION PATHWAYS

The movement of circulating lipids into peripheral tissues relies on their traversal through the endothelial cell barrier (ECB). Unlike the liver and adrenal glands, most tissues regulate lipid uptake predominantly through ECB mechanisms involving lipoprotein lipase (LPL), endothelial lipase, CD36, and other proteins, constituting a shared mechanism across various tissues [19]. Simultaneously, endothelial cells (ECs) are vulnerable to shear stress resulting from disturbed blood flow, leading to vasodilation and hypertension. This shear stress induces inflammation, heightening the risk of atherosclerosis progression [20].

Two studies indicate that the activation of Gs protein in response to shear stress plays a role in mitigating inflammation by reducing the phosphorylation of p65 (NF- $\kappa$ B) at serine 536, thereby preventing its nuclear translocation [21,22]. The involvement of Gs raised questions about an upstream GPCR receptor. In vivo evidence suggests that blocking Gs/G $\alpha$ s increases the risk of disturbed blood flow-induced atherosclerosis. Consequently, researchers investigated the expression of several GPRs associated with either the Gs subunit or orphan GPRs using bovine arterial endothelial cells (BACE) and human umbilical vein endothelial cells [22].

Surprisingly, siRNA-induced knockdown of GPR146 resulted in increased p65 phosphorylation at S536, similar to the knockdown of the Gs subunit [22]. However, blocking the Gs subunit exerts its effect on p65 phosphorylation *via* cAMP response element-binding protein (CREB) phosphorylation, whereas knockdown of GPR146 operates independently of CREB [22]. This suggests an alternative mechanism, independent of CREB and the Gs subunit, in regulating endothelial inflammation by GPR146 (Fig. 3). This study underscores that GPR146 is expressed in endothelial cells, and its downstream effects are independent of Gs/G $\alpha$ s and cAMP. However, the activation of GPR146 in response to disturbed blood flow remains unclear. Additionally, the question of whether *GPR146* plays a role in channeling lipids at the ECB remains to be explored.

## DECODING THE ENIGMA: DEORPHANIZING G PROTEIN-COUPLED RECEPTOR 146 AND UNRAVELING ITS SIGNIFICANCE

Despite the significance of GPR146 in regulating plasma lipids and the development of multiple advanced *in vivo* and *in vitro* models [4,5,23], it remains an orphan receptor which renders the understanding of its downstream effectors limited. The key considerations in deorphanizing GPCRs include: ligand binding activation, association of G-coupled proteins, signal transduction and downstream effectors, and feedback mechanisms.

Study by Yosten *et al.* in 2013 proposed the C-peptide as a ligand for GPR146, measuring cFos as a readout in a human gastric carcinoma cell line (KATOIII cells) [24]. Incubating KATOIII cells, with endogenous GPR146 expression, demonstrated increased cFos in response to C-peptide. However, Lindfors *et al.* in 2020, refuted this finding by conducting a similar experiment in Chinese hamster ovary cells (CHO-K1) with human GPR146 overexpression and using dynamic mass distribution (DMR) and  $\beta$ -arrestin recruitment as readouts [25]. Meanwhile, Han *et al.* fractionated fetal bovine serum using a 3kDa filter and incubated it with human embryonic kidney cells (HEK293) overexpressing human GPR146, measuring cAMP response elements as a readout. This suggested that GPR146 is a functional GPCR with an endogenous ligand present in serum [5].

Notably, the various approaches to deorphanizing GPR146 primarily focus on the activating ligand and downstream effectors or feedback mechanisms. As these observations stem from different cell types (tissue of origin), determining relevance is challenging due to potential tissue-dependent signaling transduction of GPR146. A recent study by Kaczmarek *et al.* elucidated the G-proteins associated with GPR146 [24]. They utilized bioluminescence resonance energy transfer (BRET) sensors to quantitatively monitor G protein-coupled receptors (GPCRs) and  $\beta$ -arrestin trafficking. Firstly, by overexpressing human GPR146 in HEK293 cells, a reduction in cAMP levels was observed. Secondly, using the BRET assay, GPR146 overexpression led to increased dissociation of  $G_{\alpha i}$  and  $G_{\beta\gamma}$ , constituting  $G_i$  coupling. The majority of  $G_i$  coupling was localized to the endosomes and the plasma membrane [18].

## CONCLUSION

In conclusion, the intricate interplay of human genetic studies and mouse experiments highlights

the multifaceted role of GPR146 in lipid metabolism and cardiometabolic health. Human findings, particularly the associations between GPR146 variants and plasma lipid levels, provide a foundation for understanding potential therapeutic interventions. The seamless transition to mouse studies reinforces and extends these genetic associations. GPR146's hepatic inhibition in mice emerges as a robust strategy against hypercholesterolemia and atherosclerosis, showcasing its therapeutic potential. Beyond VLDL regulation in the liver, GPR146 may influence adipocyte differentiation, lipolysis, and endothelial inflammation. As efforts to deorphanize GPR146, the identification of potential ligands and downstream effects expands therapeutic possibilities. GPR146's enrichment in adipose tissue adds complexity to its cardiovascular influence. In its entirety, GPR146 represents a promising and versatile target for innovative lipid-lowering strategies and cardiovascular interventions. The combination of genetic insights, functional studies, and the bridging of human and mouse research collectively contribute to a deeper understanding of GPR146's significance in the complex landscape of cardiovascular and metabolic diseases.

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## Conflicts of interest

There are no conflicts of interest.

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- of special interest
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