

# The GPR124-Wnt-PPAR $\gamma$ regulatory axis: Molecular mechanisms and therapeutic implications in chronic inflammatory diseases (Review)

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**Abstract.** G protein-coupled receptor 124 (GPR124) and peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) constitute two mechanistically distinct signaling molecules that exhibit functional convergence through their opposing regulation of the canonical Wnt/ $\beta$ -catenin pathway, thereby establishing a critical regulatory network governing inflammatory homeostasis and tissue repair responses. The present comprehensive review elucidates the molecular architecture and pathophysiological significance of the GPR124-Wnt-PPAR $\gamma$  regulatory axis, with particular emphasis on its therapeutic implications in chronic inflammatory diseases. GPR124, originally identified as an adhesion G protein-coupled receptor essential for central nervous system angiogenesis and blood-brain barrier integrity, functions as a context-dependent co-activator of Wnt7a/Wnt7b signaling. By contrast, PPAR $\gamma$ , a ligand-activated nuclear receptor and master regulator of metabolism and inflammation, exerts potent antagonistic effects on Wnt/ $\beta$ -catenin signaling through direct  $\beta$ -catenin degradation mechanisms. The opposing regulation of Wnt signaling by these two receptors establishes a molecular framework that critically influences disease progression in atherosclerosis, diabetic complications, neuroinflammation and cancer-associated inflammation, with its function being fine-tuned by tissue-specific expression patterns and diverse

mechanisms. Understanding the GPR124-Wnt-PPAR $\gamma$  axis provides novel therapeutic opportunities for combination targeting strategies in chronic inflammatory conditions, where the balance between pro-angiogenic Wnt activation and anti-inflammatory PPAR $\gamma$  signaling determines disease outcomes. The present review examines the molecular architecture of GPR124-PPAR $\gamma$  crosstalk, analyzes pathophysiological implications across multiple organ systems, and evaluates emerging therapeutic strategies for targeting this regulatory network in chronic inflammatory diseases.

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## 1. Introduction

Chronic inflammatory diseases represent a major global health burden, encompassing conditions such as atherosclerosis, type 2 diabetes mellitus, inflammatory bowel disease and neuroinflammatory disorders (1,2). These pathologies share common molecular mechanisms involving dysregulated inflammatory responses, altered cellular metabolism and compromised vascular integrity. The identification of regulatory networks that coordinate these seemingly disparate processes has emerged as a critical priority for developing more effective therapeutic interventions.

Contemporary advances in molecular and cellular biology have identified a previously uncharacterized regulatory network linking two functionally distinct classes of signaling molecules: G protein-coupled receptor 124 (GPR124), which is an adhesion G protein-coupled receptor, and peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), which is a ligand-activated nuclear receptor (3,4). Converging experimental evidence

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*Abbreviations:* BBB, blood-brain barrier; CNS, central nervous system; GPR124, G protein-coupled receptor 124; PPAR $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$

*Key words:* GPR124, PPAR $\gamma$ , Wnt signaling, chronic inflammation, atherosclerosis, diabetic complications

has demonstrated their mechanistic interconnection through differential regulation of the canonical Wnt/ $\beta$ -catenin signaling cascade, establishing the 'GPR124-Wnt-PPAR $\gamma$  regulatory axis'. This molecular framework exhibits notable implications for understanding and therapeutically targeting chronic inflammatory pathologies characterized by dysregulated tissue homeostasis and aberrant inflammatory resolution. GPR124, also known as tumor endothelial marker 5 (TEM5) and adhesion G protein-coupled receptor A2, was initially reported to serve an essential role in central nervous system (CNS) vascularization and blood-brain barrier (BBB) formation (5,6). Subsequent research has revealed broader expression patterns and functions for GPR124, including roles in peripheral angiogenesis, diabetic complications and inflammatory responses (7). The receptor functions as a highly specific co-activator for Wnt7a and Wnt7b ligands, forming a ternary complex with the GPI-anchored protein RECK to potentiate canonical Wnt/ $\beta$ -catenin signaling (8,9).

PPAR $\gamma$ , conversely, represents one of the most extensively studied nuclear receptors, renowned for its role as a master regulator of adipogenesis, glucose homeostasis and anti-inflammatory responses (10,11). The therapeutic importance of PPAR $\gamma$  is underscored by the clinical success of thiazolidinediones, a class of PPAR $\gamma$  agonists, in treating type 2 diabetes and the ongoing development of selective PPAR $\gamma$  modulators (SPPAR $\gamma$ M) for primary biliary cholangitis, nonalcoholic steatohepatitis (NASH) and other inflammatory conditions (12,13). Notably, PPAR $\gamma$  functions as a potent antagonist of Wnt/ $\beta$ -catenin signaling through direct protein-protein interactions that promote  $\beta$ -catenin degradation (14).

The opposing effects of GPR124 and PPAR $\gamma$  on Wnt signaling create a molecular switch that governs cellular responses to inflammatory stimuli, metabolic stress and vascular injury (15). This regulatory mechanism has particular relevance for chronic inflammatory diseases, where the balance between pro-angiogenic, proliferative responses mediated by Wnt activation, and anti-inflammatory, metabolic regulatory responses mediated by PPAR $\gamma$  determines disease progression and therapeutic responsiveness.

The present comprehensive review examines the molecular mechanisms underlying GPR124-PPAR $\gamma$  axis function, analyzes its pathophysiological importance in major chronic inflammatory diseases, and evaluates emerging therapeutic strategies that target this regulatory network. In addition, a critical assessment of current knowledge gaps is provided and future research directions that are needed to translate mechanistic insights into clinical applications are outlined.

## 2. Molecular architecture of the GPR124-Wnt-PPAR $\gamma$ axis

*GPR124: Structure, function and signaling mechanisms.* GPR124 is classified within the adhesion subfamily of G protein-coupled receptors, and is distinguished by its complex modular architecture comprising an exceptionally large N-terminal extracellular domain containing multiple leucine-rich repeats, immunoglobulin-like domains and hormone receptor motifs, coupled to a canonical seven-transmembrane spanning region (16). This distinctive structural organization confers dual functionality, enabling the receptor

to simultaneously mediate cell-cell adhesive interactions and transduce intracellular signaling cascades, thereby reflecting its bifunctional roles in both intercellular communication and signal transduction processes (9).

The physiological significance of GPR124 was first established through genetic studies demonstrating its absolute requirement for CNS angiogenesis and BBB formation (9,17). Global or endothelial-specific deletion of the *GPR124* gene results in embryonic lethality associated with profound CNS-specific vascular defects, including delayed vascular penetration into neural tissue, formation of pathological glomeruloid structures and widespread cerebral hemorrhage (5). These defects are accompanied by failure to establish BBB properties, as evidenced by loss of glucose transporter 1 (Glut1) expression and increased vascular permeability (18).

The molecular mechanism underlying GPR124 function involves its role as a ligand-specific co-receptor for canonical Wnt signaling (19). GPR124 forms a cell-surface complex with the GPI-anchored protein RECK, and this GPR124/RECK complex serves as a highly specific co-receptor for Wnt7a and Wnt7b ligands (20). The complex facilitates the binding and presentation of Wnt7a/b to the primary Wnt receptor complex consisting of Frizzled family receptors and low-density lipoprotein receptor-related protein (LRP)5/6 co-receptors, thereby potentiating canonical Wnt/ $\beta$ -catenin signaling (21).

Notably, GPR124 function exhibits marked context dependency. While essential for developmental angiogenesis, conditional knockout studies have revealed that GPR124 is largely dispensable for maintaining adult vascular homeostasis under physiological conditions (17,22). However, it is markedly activated in response to pathological stress, including ischemic injury, tumor growth and inflammatory challenges (17). This stress-responsive activation pattern positions GPR124 as a critical mediator of adaptive vascular responses in disease states.

*PPAR $\gamma$ : Nuclear receptor function and anti-inflammatory mechanisms.* PPAR $\gamma$  represents a ligand-activated transcription factor belonging to the nuclear receptor superfamily (23). This receptor exists in multiple isoforms generated through alternative promoter usage and splicing, with PPAR $\gamma$ 1 showing broad tissue distribution and PPAR $\gamma$ 2 being predominantly expressed in adipose tissue (24). Upon ligand binding, PPAR $\gamma$  undergoes conformational changes that promote heterodimerization with retinoid X receptor and subsequent binding to PPAR response elements in target gene promoters (25).

The anti-inflammatory repertoire of PPAR $\gamma$  encompasses diverse mechanistic modalities that transcend conventional ligand-dependent transcriptional activation (26). These include direct transrepression mechanisms involving physical protein-protein interactions between ligand-activated PPAR $\gamma$  and pro-inflammatory transcription factors, including NF- $\kappa$ B and activator protein-1, resulting in context-dependent inhibition of inflammatory gene expression programs (27). Additionally, PPAR $\gamma$  orchestrates the transcriptional upregulation of anti-inflammatory mediators and facilitates the biosynthesis of specialized pro-resolving mediators, thereby promoting active resolution of inflammatory responses rather than mere inflammatory suppression (28).

In immune cells, PPAR $\gamma$  activation promotes anti-inflammatory macrophage polarization, enhances regulatory T-cell

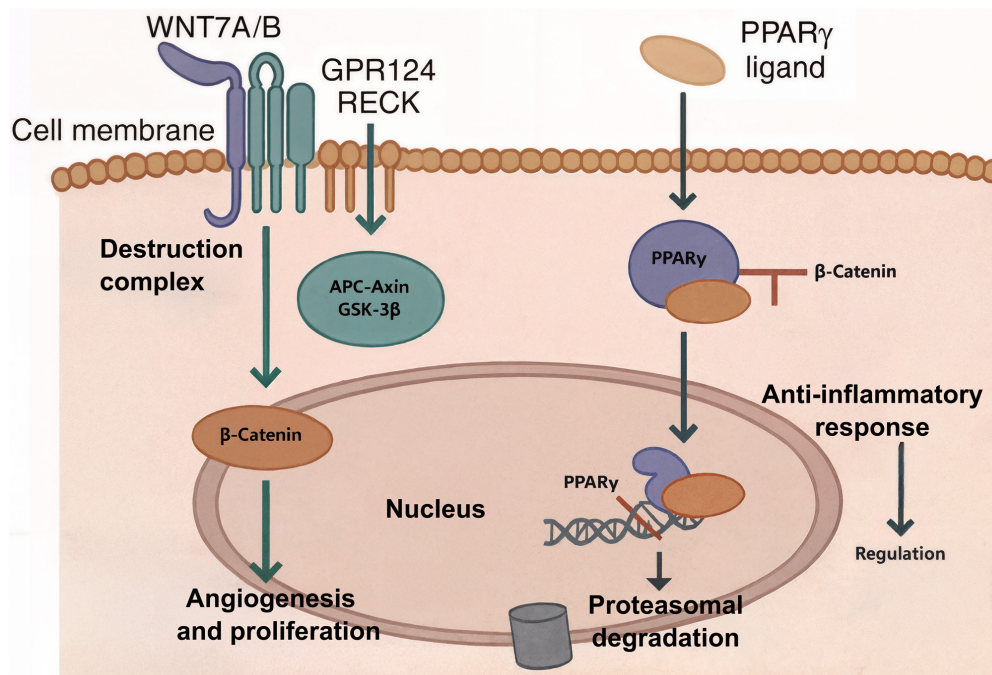


Figure 1. Molecular rheostat of the GPR124-Wnt-PPAR $\gamma$  axis. This diagram illustrates the antagonistic regulation of the canonical Wnt/ $\beta$ -catenin pathway by GPR124 and PPAR $\gamma$ . GPR124 functions as a co-activator of Wnt7a/b ligands, potentiating Wnt signaling. This leads to the inhibition of the cytoplasmic destruction complex (composed of APC, Axin and GSK-3 $\beta$ ), resulting in the stabilization and nuclear translocation of  $\beta$ -catenin. In the nucleus,  $\beta$ -catenin activates target genes that promote angiogenesis and proliferation. By contrast, ligand-activated PPAR $\gamma$  exerts potent antagonistic effects. It directly binds to  $\beta$ -catenin, facilitating its interaction with the destruction complex, and promoting its subsequent phosphorylation and proteasomal degradation. This action suppresses Wnt target gene expression, leading to anti-inflammatory responses and metabolic regulation. APC, adenomatous polyposis coli; GSK-3 $\beta$ , glycogen synthase kinase-3 $\beta$ ; GPR124, G protein-coupled receptor 124; PPAR $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$ .

function and suppresses dendritic cell activation (29). These effects are mediated through metabolic reprogramming that shifts cellular energy production from glycolysis toward oxidative phosphorylation and fatty acid oxidation, metabolic changes that are incompatible with sustained inflammatory activation (30).

*Wnt/ $\beta$ -catenin signaling: The central hub of GPR124-PPAR $\gamma$  crosstalk.* The canonical Wnt/ $\beta$ -catenin signaling pathway functions as the principal molecular convergence point mediating the functional crosstalk between GPR124 and PPAR $\gamma$  signaling networks (31,32). Under basal conditions, cytoplasmic  $\beta$ -catenin undergoes constitutive phosphorylation by a multiprotein destruction complex containing adenomatous polyposis coli (APC), Axin scaffolding proteins and glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), subsequently targeting  $\beta$ -catenin for ubiquitin-mediated proteasomal degradation and maintaining low steady-state levels (33). Wnt ligand engagement with cognate Frizzled/LRP receptor complexes disrupts this cytoplasmic destruction machinery, permitting  $\beta$ -catenin stabilization, nuclear translocation and the formation of transcriptionally active complexes with T-cell factor/lymphoid enhancer factor transcription factors (34).

GPR124-mediated potentiation of Wnt7a/b signaling results in robust  $\beta$ -catenin stabilization and nuclear accumulation, particularly in endothelial cells during angiogenic responses (19). This activation drives the expression of genes essential for vascular development, barrier function and angiogenic sprouting, including *Glut1*, *Claudin-5* and *VE-cadherin* (18).

In contrast, PPAR $\gamma$  activation leads to potent inhibition of Wnt/ $\beta$ -catenin signaling through direct protein-protein interactions (35). Ligand-activated PPAR $\gamma$  physically binds to  $\beta$ -catenin through a specific catenin-binding domain, facilitating the interaction of  $\beta$ -catenin with the destruction complex, and promoting its phosphorylation and degradation (3,36). This mechanism effectively reduces cellular  $\beta$ -catenin levels and suppresses Wnt target gene expression.

The opposing effects of GPR124 and PPAR $\gamma$  on  $\beta$ -catenin stability create a molecular rheostat that fine-tunes cellular responses to environmental stimuli. The relative activity of these pathways determines whether cells adopt pro-angiogenic, proliferative phenotypes associated with Wnt activation, or anti-inflammatory, metabolically quiescent states associated with PPAR $\gamma$  signaling (Fig. 1).

*Context-dependent pathway interactions.* The functional relationship between GPR124 and PPAR $\gamma$  exhibits marked context dependency that reflects the complex regulatory mechanisms governing their expression and activity (37,38). While the canonical Wnt/ $\beta$ -catenin pathway serves as the primary signaling nexus for this crosstalk, it is important to recognize that GPR124 can also engage other signaling pathways. This expands the functional repertoire of this receptor beyond its role as a Wnt-specific co-receptor. For example, a recent study in trophoblast cells demonstrated that GPR124 can regulate cell proliferation, migration, invasion and inflammation by modulating the JNK and P38 MAPK pathways (39). This finding not only highlights the mechanistic diversity of GPR124 signaling but also suggests that its biological functions may be broader

than previously appreciated, opening new avenues for understanding its pathophysiological significance.

During normal physiological conditions, both receptors maintain low basal activity, with GPR124 showing minimal expression in quiescent endothelium and PPAR $\gamma$  primarily active in metabolic tissues (17). Inflammatory stimuli trigger coordinated but opposing changes in pathway activity. Pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , upregulate GPR124 expression in endothelial cells while simultaneously suppressing PPAR $\gamma$  activity through post-translational modifications and coactivator sequestration (40). This creates a pro-inflammatory state characterized by enhanced Wnt signaling, increased angiogenic potential and reduced anti-inflammatory capacity. Conversely, anti-inflammatory mediators and metabolic signals promote PPAR $\gamma$  activation while suppressing GPR124-mediated Wnt signaling (15). This regulatory pattern enables dynamic switching between inflammatory and resolution phases, with the GPR124-Wnt-PPAR $\gamma$  axis serving as a central coordinator of these transitions.

Studies have also revealed tissue-specific variations in pathway interactions. In adipose tissue, GPR124 appears to facilitate early stages of adipogenesis that enable subsequent PPAR $\gamma$ -driven terminal differentiation, suggesting cooperative rather than purely antagonistic relationships in certain contexts (41). Similarly, in certain types OF cancer, aberrant Wnt signaling can paradoxically activate rather than inhibit PPAR $\gamma$ , reflecting the complex nature of pathway crosstalk in transformed cells (4).

### 3. Pathophysiological implications in chronic inflammatory diseases

*Atherosclerosis: Opposing roles in vascular inflammation.* Atherosclerosis represents a paradigmatic chronic inflammatory disease where the GPR124-Wnt-PPAR $\gamma$  axis serves crucial but opposing roles in disease progression (42). The condition is characterized by the formation of lipid-rich plaques within arterial walls, accompanied by chronic inflammation, endothelial dysfunction and progressive vascular remodeling (43).

GPR124 facilitates atherosclerotic progression through a coordinated array of pro-inflammatory and pro-atherogenic mechanisms that collectively promote vascular wall pathology (44). Enhanced GPR124 expression in atherosclerotic vessels potentiates NLR family pyrin domain containing 3 inflammasome assembly and activation, culminating in the proteolytic maturation and secretion of the inflammatory cytokines IL-1 $\beta$  and IL-18 (45). This inflammatory cascade orchestrates the recruitment and activation of circulating monocytes and their differentiation into pro-inflammatory macrophages within the arterial intima, thereby perpetuating chronic inflammatory responses that drive plaque formation and destabilization. Furthermore, GPR124-mediated Wnt signaling promotes the phenotypic modulation of vascular smooth muscle cells from a contractile to a synthetic, proliferative phenotype, facilitating their migration into the intimal space, and contributing to neointimal hyperplasia and pathological arterial remodeling (44).

The pro-angiogenic effects of GPR124 also contribute to plaque progression by promoting the formation of intraplaque neovascularization (46). These newly formed vessels are

typically immature and leaky, facilitating the infiltration of inflammatory cells and lipoproteins into the plaque core. The resulting increase in plaque inflammation and lipid accumulation promotes plaque vulnerability, and increases the risk of rupture and thrombotic complications (47).

By contrast, PPAR $\gamma$  provides robust protection against atherosclerotic development through multiple anti-inflammatory and metabolic mechanisms (42). PPAR $\gamma$  activation in macrophages promotes the alternative M2 polarization state, which is characterized by enhanced phagocytic capacity, increased production of anti-inflammatory factors, such as IL-10, TGF- $\beta$  and IL-1 receptor antagonist, and improved cholesterol efflux (48). These effects facilitate the clearance of apoptotic cells and lipid debris from atherosclerotic lesions, promoting plaque stabilization and resolution of inflammation (49).

PPAR $\gamma$  also exerts direct protective effects on endothelial cells, enhancing nitric oxide production, reducing oxidative stress and improving endothelial barrier function (42). These effects help maintain vascular homeostasis and prevent the endothelial dysfunction that initiates atherosclerotic development (50). Furthermore, PPAR $\gamma$  activation promotes the expression of genes, such as *ABCA1*, *ABCG1* and *SR-B1*, involved in reverse cholesterol transport, facilitating the removal of excess cholesterol from arterial walls (51).

The opposing roles of GPR124 and PPAR $\gamma$  in atherosclerosis suggest that the balance between these pathways critically determines disease progression. Therapeutic strategies that simultaneously inhibit GPR124-mediated pro-inflammatory signaling while enhancing PPAR $\gamma$ -mediated anti-inflammatory responses may provide synergistic benefits for atherosclerosis prevention and treatment (Fig. 2).

*Diabetic complications: Vascular protection and metabolic regulation.* Type 2 diabetes mellitus and its associated complications represent another major area where the GPR124-Wnt-PPAR $\gamma$  axis exerts notable pathophysiological influence (21). Diabetic complications, including diabetic nephropathy, retinopathy and neuropathy, involve complex interactions between metabolic dysfunction, chronic inflammation and microvascular injury (52).

Recent investigations have established GPR124 as a pivotal cytoprotective mediator in the pathogenesis of diabetic nephropathy, revealing novel mechanistic insights into podocyte preservation strategies (7,53). GPR124 expression in glomerular podocytes confers protection against diabetes-induced cellular senescence and structural injury through direct molecular interactions with the cytoskeletal protein vinculin and negative regulatory modulation of focal adhesion kinase signaling cascades (54). This cytoprotective mechanism preserves podocyte structural integrity and maintains glomerular filtration barrier selectivity, with clinical studies demonstrating positive associations between GPR124 expression levels and estimated glomerular filtration rate, alongside inverse associations with proteinuria severity, establishing GPR124 as a potential biomarker for nephroprotective therapeutic responses.

The protective effects of GPR124 in diabetic nephropathy appear to involve both direct cellular mechanisms and indirect effects mediated through Wnt signaling modulation (15).

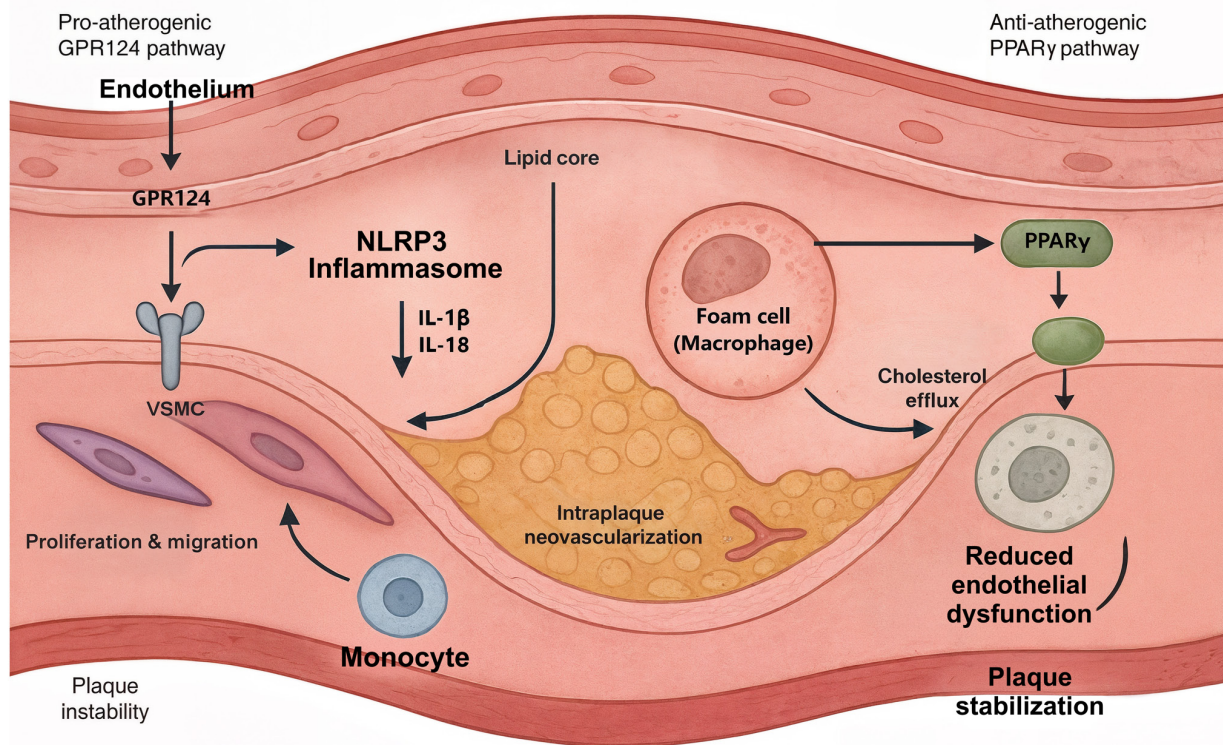


Figure 2. Opposing roles of the GPR124-PPAR $\gamma$  axis in atherosclerosis. The conflicting functions of GPR124 and PPAR $\gamma$  in the progression of atherosclerosis are presented. The pro-atherogenic GPR124 pathway shows that enhanced GPR124 expression promotes NLRP3 inflammasome activation, leading to the secretion of pro-inflammatory cytokines IL-1 $\beta$  and IL-18. This inflammatory cascade facilitates monocyte recruitment, while GPR124-mediated Wnt signaling also drives the proliferation and migration of VSMCs and stimulates intraplaque neovascularization, all contributing to plaque instability. Conversely, the anti-atherogenic PPAR $\gamma$  pathway illustrates that PPAR $\gamma$  activation promotes M2 macrophage polarization, which enhances cholesterol efflux from foam cells. PPAR $\gamma$  also exerts direct protective effects on the endothelium, reducing dysfunction, ultimately leading to plaque stabilization. GPR124, G protein-coupled receptor 124; NLRP3, NLR family pyrin domain containing 3; PPAR $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$ ; VSMCs, vascular smooth muscle cells.

GPR124-mediated Wnt activation promotes the expression of genes involved in podocyte survival and barrier function, including *NPHS1* and *Bcl-2*, while also enhancing the regenerative capacity of injured glomerular cells (55). These effects help maintain kidney function and slow the progression of diabetic nephropathy.

In diabetic retinopathy, GPR124 serves a more complex role that reflects the dual nature of angiogenic responses in this condition (56). While pathological angiogenesis contributes to vision-threatening complications, appropriate vascular responses are necessary for maintaining retinal function and preventing ischemic injury (57). GPR124-mediated regulation of retinal angiogenesis may therefore represent a therapeutic target for achieving the delicate balance between preventing pathological neovascularization while preserving physiological vascular function.

PPAR $\gamma$  provides complementary protection against diabetic complications through its master regulatory role in glucose homeostasis and insulin sensitivity (10). PPAR $\gamma$  activation improves systemic metabolic control, reducing hyperglycemia and associated oxidative stress that drives diabetic complications (58). The receptor also exerts direct protective effects on the vascular system, brain/CNS, kidneys, eyes, peripheral nerves, liver, lungs and components of the immune system, promoting anti-inflammatory responses and enhancing cellular stress resistance. Evidence includes neuroprotection and cognitive benefits in the CNS, renoprotection in

diabetic kidney disease, retinal protection in the eye, improvement of diabetic peripheral neuropathy, mitigation of hepatic steatosis/NASH, reduction of respiratory infection/inflammation and pulmonary vascular remodeling in the lung, and modulation of innate immunity (59-63).

The clinical success of the PPAR $\gamma$  agonists thiazolidinediones in reducing diabetic complications demonstrates the therapeutic potential of targeting this pathway (64). These agents not only improve glycemic control, but also provide direct organ protection through anti-inflammatory and cytoprotective mechanisms (65). The combination of GPR124-mediated vascular protection with PPAR $\gamma$ -mediated metabolic improvement suggests potential synergistic benefits for preventing and treating diabetic complications.

**Neuroinflammation: BBB integrity and neuroprotection.** Chronic neuroinflammatory diseases, including Alzheimer's disease, multiple sclerosis and Parkinson's disease, involve complex interactions between BBB dysfunction, microglial activation and neuronal injury (66). The GPR124-Wnt-PPAR $\gamma$  axis serves key roles in regulating these pathological processes through distinct but complementary mechanisms (9).

GPR124 expression and activity are indispensable for preserving BBB structural and functional integrity during acute and chronic neuroinflammatory states, representing a critical neurovascular protective mechanism (17). This protective function reflects both the fundamental developmental role

of this receptor in CNS vascularization and its stress-responsive reactivation during pathological conditions. In experimental models of ischemic cerebrovascular injury, endothelial-specific genetic ablation of GPR124 precipitates a severe BBB compromise, which is characterized by enhanced microvascular permeability, increased susceptibility to hemorrhagic transformation and markedly worse neurological functional outcomes. The underlying molecular mechanisms involve GPR124-mediated preservation of intercellular junctional complexes, including both tight junction proteins (claudin-5, occludin and zonula occludens-1) and adherens junction components (VE-cadherin and  $\beta$ -catenin), which collectively regulate paracellular permeability and maintain the selective barrier properties essential for CNS homeostasis (20).

The protective effects of GPR124 on BBB function involve the maintenance of tight junction proteins and adherens junction complexes that regulate paracellular permeability (67). GPR124-mediated Wnt signaling promotes the expression of claudin-5, occludin and VE-cadherin, essential components of the BBB structure (68,69). Additionally, GPR124 activation enhances the expression of specific transporters such as Glut1 that are required for BBB function (17).

During chronic neuroinflammation, BBB dysfunction facilitates the infiltration of peripheral immune cells and inflammatory mediators into the CNS, exacerbating neuronal injury and disease progression (70). GPR124-mediated preservation of barrier integrity thus provides a critical protective mechanism against neuroinflammatory progression (71). Beyond its direct structural effects on endothelial tight junctions, this barrier-protective function indirectly regulates neuroinflammation by physically limiting the infiltration of peripheral immune cells into the CNS parenchyma (17). Whether GPR124 on endothelial or perivascular cells also directly modulates the expression of adhesion molecules or chemokines involved in immune cell trafficking remains an important area for future investigation.

PPAR $\gamma$  contributes to neuroprotection through powerful anti-inflammatory and antioxidant mechanisms (72). PPAR $\gamma$  activation in microglia promotes the anti-inflammatory M2 polarization state, reducing the production of neurotoxic cytokines, and enhancing the clearance of protein aggregates and cellular debris (73). These effects help resolve neuroinflammation and create a supportive environment for neuronal survival and repair (66).

PPAR $\gamma$  also exerts direct neuroprotective effects on neurons and oligodendrocytes, enhancing cellular stress resistance and promoting survival signaling pathways (74). The role of this receptor in regulating mitochondrial function and oxidative metabolism provides additional protection against the energetic stress that characterizes numerous neurodegenerative diseases (75).

The combination of GPR124-mediated BBB protection and PPAR $\gamma$ -mediated neuroinflammation resolution represents a promising therapeutic approach for chronic neuroinflammatory diseases. This dual targeting strategy could address both the vascular and inflammatory components of neurodegeneration, potentially providing superior neuroprotective outcomes compared with single-pathway interventions (Fig. 3).

*Cancer-associated inflammation: Tumor angiogenesis and immune evasion.* Cancer-associated inflammation

represents a complex pathophysiological process where the GPR124-Wnt-PPAR $\gamma$  axis exerts context-dependent effects on tumor progression, angiogenesis and immune responses (76). The chronic inflammatory microenvironment within tumors involves dynamic interactions between cancer cells, stromal cells, immune cells and blood vessels, which collectively determine tumor growth and metastatic potential (77).

GPR124 contributes to tumor progression primarily through its pro-angiogenic functions in tumor endothelium (22). Originally identified as TEM5, GPR124 shows elevated expression in tumor vasculature compared with in normal tissues (78). This enhanced expression facilitates tumor angiogenesis by promoting endothelial cell proliferation, migration and tube formation in response to Wnt7a/b ligands secreted by tumor cells (79).

Previous studies have revealed additional roles for GPR124 in cancer cell biology beyond its endothelial functions (20). In glioblastoma, GPR124 regulates cancer cell proliferation through its effects on microtubule assembly and mitotic progression (80). The interaction of the receptor with centrosome proteins affects chromosome segregation and cell cycle progression, contributing to the rapid proliferation that is characteristic of aggressive brain tumors (81).

GPR124 also influences tumor-associated inflammation through effects on immune cell recruitment and activation (82). Enhanced GPR124 signaling in tumor-associated macrophages promotes the pro-tumorigenic M2 polarization state, facilitating tumor immune evasion and creating a supportive microenvironment for cancer progression (83,84). This influence on TAMs suggests a broader role for GPR124 in shaping the tumor immune microenvironment beyond angiogenesis (21). Its potential involvement in stromal remodeling or the recruitment of other immunosuppressive cell populations, such as myeloid-derived suppressor cells (MDSCs), remains an underexplored area that warrants further investigation to fully understand its contribution to cancer-associated inflammation and immune evasion.

PPAR $\gamma$  demonstrates multifaceted and context-dependent regulatory functions in cancer-associated inflammatory processes (13,85), exhibiting both tumor-suppressive and, paradoxically, tumor-promoting activities depending on the specific cellular context, tumor microenvironment and disease stage. In solid malignancies, such as endometrial cancer, melanoma and breast cancer, PPAR $\gamma$  functions as a bona fide tumor suppressor through its coordinated anti-proliferative, pro-apoptotic and pro-differentiation effects on transformed cells (13). PPAR $\gamma$  activation induces cell cycle arrest at critical checkpoints, enhances apoptotic susceptibility through both intrinsic and extrinsic pathways, and promotes terminal cellular differentiation programs that antagonize the dedifferentiated phenotype characteristic of aggressive malignancies (86). Concurrently, the anti-inflammatory properties of PPAR $\gamma$  contribute to the resolution of tumor-promoting chronic inflammation by suppressing the production of growth-stimulatory cytokines, angiogenic factors and tissue remodeling enzymes that collectively support neoplastic progression and metastatic dissemination (87). However, research has revealed that PPAR $\gamma$  can also contribute to cancer progression under certain conditions (88). In established tumors, PPAR $\gamma$  activation may promote metabolic reprogramming that supports

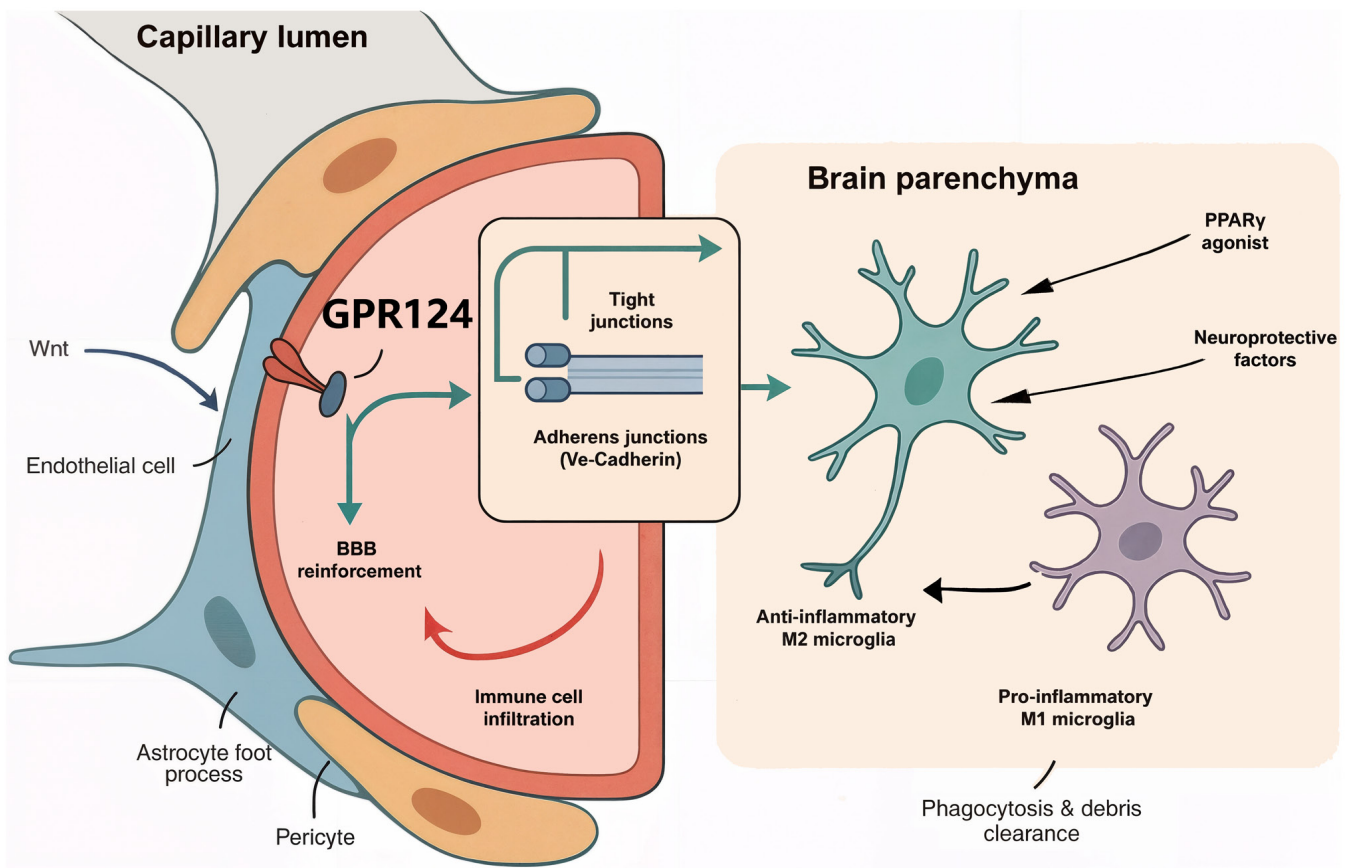


Figure 3. Complementary protective mechanisms of GPR124 and PPAR $\gamma$  in the neurovascular unit. The synergistic roles of GPR124 and PPAR $\gamma$  in maintaining central nervous system homeostasis. GPR124, expressed on endothelial cells, is essential for BBB integrity. Wnt signaling via GPR124 reinforces the BBB by promoting the expression of tight junction proteins (such as claudin-5 and occludin) and adherens junction proteins (including VE-cadherin), thereby inhibiting the infiltration of peripheral immune cells. Within the brain parenchyma, PPAR $\gamma$  activation is shown to be neuroprotective. It promotes the polarization of microglia to an anti-inflammatory M2 phenotype, which enhances the phagocytosis of debris and increases the production of neuroprotective factors, thus resolving neuroinflammation. BBB, blood-brain barrier; GPR124, G protein-coupled receptor 124; PPAR $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$ .

cancer cell survival and drug resistance (89). Furthermore, PPAR $\gamma$  can mediate tumor adaptation to immunotherapy through the regulation of immunosuppressive factors such as vascular endothelial growth factor-A and the expansion of MDSCs (90).

The dual roles of PPAR $\gamma$  in cancer highlight the importance of understanding context-dependent pathway functions when developing therapeutic strategies. The interaction between GPR124-mediated pro-angiogenic signaling and PPAR $\gamma$ -mediated metabolic regulation may determine whether tumors adopt aggressive, highly vascularized phenotypes or more indolent, metabolically adapted states.

#### 4. Therapeutic implications and clinical translation

*Single-pathway targeting strategies.* The distinct roles of GPR124 and PPAR $\gamma$  in chronic inflammatory diseases provide multiple opportunities for therapeutic intervention through single-pathway targeting approaches. These strategies leverage the specific functions of each receptor to address particular aspects of disease pathology while minimizing off-target effects.

*GPR124 modulation.* GPR124 represents an attractive therapeutic target due to its context-dependent essentiality and restricted expression pattern (17). The requirement for

this receptor primarily during developmental or pathological stress conditions suggests that therapeutic modulation could provide notable benefits while minimizing effects on normal physiological processes.

For conditions requiring enhanced vascular integrity, such as stroke or diabetic complications, GPR124 activation represents a logical therapeutic strategy (17). Engineered Wnt surrogate molecules designed to specifically activate the GPR124/RECK receptor complex are currently under development for treating vascular retinopathies (91). These agents could potentially be adapted for other conditions requiring BBB protection or enhanced vascular stability.

The development of GPR124 agonists faces several technical challenges, including the complexity of the signaling mechanisms of the receptor and the need for tissue-specific targeting (92). Current approaches focus on small molecules that enhance GPR124/RECK complex formation or peptide-based agents derived from the extracellular domain of the receptor (44).

Conversely, GPR124 inhibition may be beneficial in conditions where excessive angiogenesis or Wnt signaling contributes to pathology, such as certain types of cancer or proliferative retinopathies (93). Therapeutic antibodies targeting GPR124 or small molecule inhibitors that disrupt receptor function are being investigated for anti-angiogenic applications (94).

**PPAR $\gamma$  targeting.** PPAR $\gamma$  represents one of the most clinically validated therapeutic targets in metabolism and inflammation, with multiple approved drugs and an active development pipeline (10). The clinical success of thiazolidinediones in treating type 2 diabetes demonstrates the therapeutic potential of PPAR $\gamma$  activation, while ongoing research explores applications in cancer, neurodegeneration and inflammatory diseases (95).

Advances in PPAR $\gamma$  drug development focus on selective modulators that retain beneficial anti-inflammatory and insulin-sensitizing effects while minimizing adverse metabolic consequences such as weight gain and fluid retention (96). These SPPAR $\gamma$ Ms achieve improved therapeutic profiles through differential coactivator recruitment and tissue-specific gene expression patterns (97).

Notable recent approvals include seladelpar for primary biliary cholangitis and the advanced development of lanifibranor for NASH (98). These successes demonstrate the continued clinical relevance of PPAR $\gamma$  targeting and the potential for expansion into additional inflammatory conditions.

For chronic inflammatory diseases, PPAR $\gamma$  agonists provide broad anti-inflammatory effects that address multiple aspects of disease pathology (99). The ability of the receptor to promote inflammation resolution, enhance tissue repair and improve metabolic function makes it particularly attractive for conditions involving chronic inflammation and metabolic dysfunction (100).

Despite these pharmacological advances, achieving optimal tissue-specific targeting and maintaining an ideal therapeutic index that maximizes beneficial effects while minimizing adverse consequences remains a formidable challenge in contemporary PPAR $\gamma$  modulator development. Addressing these limitations necessitates innovative approaches encompassing both rational ligand design strategies and sophisticated drug delivery methodologies. Promising avenues include the development of covalent modulators designed to selectively engage tissue-resident co-regulatory proteins, implementation of targeted delivery systems utilizing antibody-drug conjugates or engineered nanoparticle carriers, and exploitation of tissue-specific promoter elements for localized therapeutic agent expression (101,102). Such progressive strategies represent essential innovations required to identify the complete therapeutic potential of PPAR $\gamma$  modulation while achieving superior safety profiles and enhanced patient tolerability across diverse clinical applications.

**Combination targeting strategies.** The opposing regulation of Wnt signaling by GPR124 and PPAR $\gamma$  provides a compelling rationale for combination therapeutic approaches that target both pathways simultaneously (37). Such strategies could achieve synergistic benefits by addressing multiple aspects of disease pathology while potentially reducing the required doses of individual agents.

**Dual pathway targeting.** In diseases characterized by excessive Wnt signaling and inadequate anti-inflammatory responses, such as certain types of cancer or atherosclerosis, combination strategies involving GPR124 inhibition and PPAR $\gamma$  activation could provide synergistic benefits (44). This therapeutic paradigm is predicated upon the mechanistically

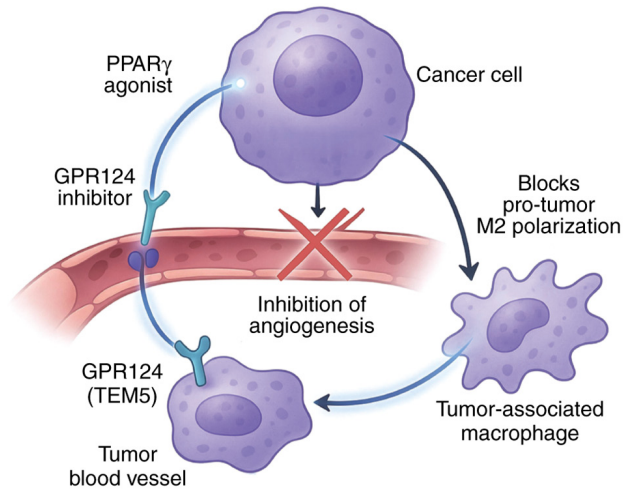


Figure 4. A combination therapeutic strategy targeting the GPR124-Wnt-PPAR $\gamma$  axis in cancer. A dual-targeting strategy for cancer treatment, which is particularly relevant for diseases such as atherosclerosis or certain types of cancer characterized by excessive Wnt signaling, is conceptualized. The strategy involves two simultaneous interventions. First, a GPR124 inhibitor blocks GPR124 (also known as TEM5) on tumor endothelial cells, thereby inhibiting Wnt7-driven tumor angiogenesis. Second, a PPAR $\gamma$  agonist exerts multiple antitumor effects. It directly acts on cancer cells to induce cell cycle arrest and apoptosis, and also acts on tumor-associated macrophages to block their pro-tumorigenic M2 polarization, thus resolving tumor-promoting inflammation. This combination approach provides a synergistic attack on the tumor microenvironment.

sound hypothesis that concurrent suppression of pro-angiogenic and pro-proliferative Wnt signaling cascades, combined with pharmacological enhancement of anti-inflammatory and pro-resolution PPAR $\gamma$  pathways, will generate synergistic therapeutic benefits that exceed the additive effects of individual pathway modulation. The theoretical advantages of such dual-targeting approaches encompass enhanced comprehensive pathway modulation, the reduced likelihood of the development of compensatory resistance mechanisms, and the potential for dose reduction strategies that minimize individual agent-associated toxicities while maintaining therapeutic efficacy. Additionally, this combinatorial targeting strategy addresses the temporal dynamics of disease progression, wherein GPR124 inhibition provides immediate effects on pathological angiogenesis and cellular proliferation, while PPAR $\gamma$  activation delivers sustained anti-inflammatory benefits and promotes active resolution of chronic inflammatory states (Fig. 4).

**Sequential pathway modulation.** For conditions involving phases of tissue injury followed by repair and resolution, sequential modulation of the GPR124-Wnt-PPAR $\gamma$  axis may provide optimal therapeutic outcomes (15). This approach would involve initial GPR124 activation to promote vascular integrity and tissue survival during acute injury phases, followed by PPAR $\gamma$  activation to enhance inflammation resolution and tissue remodeling during recovery phases.

Stroke represents a paradigmatic example where sequential targeting could be beneficial (103). Early GPR124 activation could help maintain BBB integrity and prevent hemorrhagic transformation, while delayed PPAR $\gamma$  activation could promote neuroinflammation resolution and enhance long-term recovery (19).

**Precision medicine approaches.** The inherently context-dependent and patient-specific variability in GPR124-PPAR $\gamma$  axis functionality strongly supports the implementation of precision medicine strategies that incorporate comprehensive individual patient phenotyping to optimize therapeutic selection and clinical outcomes (22). Such personalized therapeutic approaches should integrate multiple determinants of treatment responsiveness, including genetic polymorphism profiles, epigenetic modifications, biomarker signatures reflecting pathway activity states and disease-specific pathophysiological considerations. The convergence of pharmacogenomic insights, advanced biomarker discovery platforms and real-time therapeutic monitoring technologies creates unprecedented opportunities for implementing truly individualized treatment paradigms that maximize therapeutic efficacy while minimizing adverse effects across diverse patient populations with chronic inflammatory diseases.

**Genetic variants and pharmacogenomics.** Genetic variants in *GPR124* and *PPAR $\gamma$*  markedly influence receptor function and therapeutic responsiveness (104). *PPAR $\gamma$*  polymorphisms, particularly the Pro12Ala variant, affect insulin sensitivity, cardiovascular risk and response to thiazolidinedione therapy (105). Similarly, *GPR124* variants may influence vascular development, BBB function and susceptibility to neurovascular diseases (106).

Future therapeutic approaches could incorporate genetic testing to guide treatment selection and dosing strategies. Patients with specific genetic profiles might benefit from particular combinations of GPR124 and PPAR $\gamma$  modulators, while others might require alternative therapeutic approaches (107).

**Biomarker-guided therapy.** The development of biomarkers reflecting GPR124 and PPAR $\gamma$  pathway activity could enable real-time monitoring of therapeutic responses and guide treatment adjustments (107). Potential biomarkers include circulating levels of Wnt signaling components, *PPAR $\gamma$*  target gene expression profiles and imaging-based assessments of vascular function (15).

Advanced imaging techniques could provide non-invasive assessment of BBB integrity, tissue perfusion and inflammatory activity, enabling personalized treatment monitoring and optimization. These approaches could help identify patients most likely to benefit from specific therapeutic interventions and guide treatment duration and intensity.

**Challenges, safety and tolerability considerations.** Despite the promising therapeutic potential of targeting the GPR124-Wnt-PPAR $\gamma$  axis, several challenges, particularly regarding drug development, safety and tolerability, must be addressed for successful clinical translation.

**Drug development challenges.** GPR124 represents a relatively novel therapeutic target with limited pharmaceutical investment and few available chemical tools (92). The development of selective GPR124 modulators requires notable investment in drug discovery and optimization, including structure-activity relationship studies, selectivity profiling and pharmacokinetic optimization. The complex signaling mechanisms of GPR124, involving interactions with RECK and specific Wnt ligands, present additional challenges for designing drugs that achieve

appropriate selectivity for GPR124/RECK-mediated signaling while avoiding unintended effects on other Wnt pathway components (108).

**Safety, tolerability and off-target effects.** The pharmacological modulation of these fundamental homeostatic pathways necessitates comprehensive safety assessment frameworks that thoroughly evaluate potential on-target adverse effects, off-target toxicities and complex drug-drug interactions inherent to combination therapeutic regimens.

For PPAR $\gamma$ -targeting agents, the clinical utility of full receptor agonists, exemplified by the thiazolidinedione class, remains constrained by notable mechanism-based adverse effects, including excessive adipogenesis-mediated weight gain, fluid retention leading to peripheral edema and potential heart failure exacerbation, and increased fracture risk attributed to osteoblast function impairment (109). While SPPAR $\gamma$ Ms represent a pharmacological advancement designed to mitigate these dose-limiting toxicities, complete dissociation of therapeutic benefits from adverse metabolic consequences has not been fully achieved in clinical practice, highlighting the need for continued drug development innovations.

GPR124 modulation also presents theoretical safety concerns that require careful evaluation. Given the essential role of the receptor in CNS vascularization, systemic or long-term inhibition could have unintended consequences on vascular function (19) and tissue perfusion, particularly in patients with underlying vascular comorbidities (17). Conversely, therapeutic activation of GPR124 must be carefully controlled to avoid promoting pathological angiogenesis, a concern in conditions such as cancer-associated inflammation or proliferative retinopathies (22,110).

Finally, combination therapies, while theoretically synergistic, present additional complexity for safety assessment. Rigorous preclinical evaluation is required to investigate potential drug-drug interactions, additive toxicities and the emergence of novel adverse effects that may not be apparent in single-agent studies.

## 5. Future directions and research priorities

**Mechanistic understanding.** Despite notable advances in understanding GPR124 and PPAR $\gamma$  functions, several critical knowledge gaps remain that limit therapeutic development. Priority areas for future research include detailed characterization of tissue-specific signaling mechanisms, identification of additional pathway components and elucidation of disease-specific regulatory networks.

The molecular basis for context-dependent pathway interactions requires further investigation. Understanding how the cellular environment, inflammatory stimuli and metabolic status influence GPR124-PPAR $\gamma$  crosstalk will be essential for predicting therapeutic responses and optimizing treatment strategies.

Advanced methodological approaches, including single-cell RNA sequencing (scRNA-seq), spatial transcriptomics and real-time pathway monitoring, may provide novel insights into pathway dynamics and regulatory mechanisms (111). These technologies will enable detailed characterization of cell-type-specific pathway functions and temporal patterns of pathway activation during disease progression.

Furthermore, comprehensive preclinical validation studies are critically required to substantiate the theoretical synergistic potential of dual GPR124/PPAR $\gamma$  modulation strategies and to establish their translational feasibility for clinical development. These investigations should employ state-of-the-art methodological approaches, including scRNA-seq for cellular heterogeneity analysis, spatial transcriptomics for tissue architecture-function relationships, and functional genomics assays in disease-relevant organoid models and genetically modified animal systems. Such systematic preclinical evaluation is essential to confirm mechanistic plausibility, quantify therapeutic synergy indices, identify optimal dosing combinations, characterize pharmacokinetic and pharmacodynamic interactions, and proactively identify potential safety signals before clinical translation can be responsibly pursued.

*Therapeutic development.* The translation of mechanistic insights into clinical therapies requires coordinated efforts in drug discovery, preclinical validation and clinical development. Priority areas include the development of selective GPR124 modulators, optimization of PPAR $\gamma$ -targeting strategies and validation of combination therapeutic approaches.

Collaborative efforts between academic institutions, pharmaceutical companies and regulatory agencies will be essential for advancing GPR124-targeting therapeutics through clinical development. The establishment of standardized assays, validated animal models and clinical biomarkers will facilitate therapeutic development and regulatory approval.

*Clinical translation.* The successful clinical translation of GPR124-PPAR $\gamma$  targeting strategies will require careful patient selection, biomarker development and clinical trial design. Initial clinical studies should focus on diseases with a clear mechanistic rationale and measurable clinical endpoints, such as diabetic complications or stroke prevention.

The development of companion diagnostics and biomarker-guided treatment algorithms will be essential for implementing precision medicine approaches. These tools will enable the identification of patients most likely to benefit from specific therapeutic interventions and provide objective measures of treatment response.

## 6. Conclusion

The GPR124-Wnt-PPAR $\gamma$  regulatory axis constitutes a fundamental molecular rheostat that governs the dynamic equilibrium between pro-inflammatory, pro-angiogenic cellular responses, and anti-inflammatory, metabolic homeostatic programs in chronic inflammatory disease pathogenesis. This comprehensive review has systematically examined the complex molecular architecture underlying this regulatory network, elucidated its pathophysiological importance across multiple disease paradigms and critically evaluated emerging therapeutic opportunities for clinical translation. The antagonistic regulation of Wnt/ $\beta$ -catenin signaling by GPR124 and PPAR $\gamma$  establishes a molecular switch mechanism that determines cellular fate decisions in response to inflammatory stimuli, metabolic perturbations and tissue injury signals, thereby providing novel mechanistic insights into the pathogenesis of atherosclerosis, diabetic complications,

neuroinflammatory disorders and cancer-associated inflammatory processes.

The opposing effects of GPR124 and PPAR $\gamma$  on Wnt/ $\beta$ -catenin signaling create a molecular switch that determines cellular responses to inflammatory stimuli, metabolic stress and tissue injury. Understanding this regulatory mechanism provides novel insights into the pathogenesis of atherosclerosis, diabetic complications, neuroinflammation and cancer-associated inflammation. The context-dependent nature of pathway interactions explains how the same molecular components can contribute to both protective and pathological responses depending on the cellular environment and disease stage.

The therapeutic implications of targeting the GPR124-Wnt-PPAR $\gamma$  axis are substantial, encompassing both single-pathway and combination targeting strategies. While PPAR $\gamma$  represents a clinically validated target with multiple approved therapies, GPR124 remains an emerging target with significant untapped potential. The development of selective GPR124 modulators and optimized combination therapies could provide new treatment options for chronic inflammatory diseases that inadequately respond to current interventions.

Future research priorities include detailed mechanistic characterization of pathway interactions, development of selective therapeutic agents, and validation of combination targeting strategies in preclinical and clinical studies. The successful translation of these research advances into clinical applications will require coordinated efforts across multiple disciplines and stakeholders.

The GPR124-Wnt-PPAR $\gamma$  axis represents a promising frontier for understanding and treating chronic inflammatory diseases. As the mechanistic understanding regarding this axis advances and therapeutic tools improve, this regulatory network may provide the foundation for next-generation precision medicine approaches that address the complex, multifactorial nature of chronic inflammatory pathology.

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## Availability of data and materials

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## Authors' contributions

MWC wrote the original draft of the manuscript, conceptualized the study, conducted the investigation (i.e., the review and analysis of literature and data), designed the methodology and created the visualizations (figures). SYT reviewed and edited the manuscript, contributed to the use of software tools

(Endnote reference management), helped with the creation of visualizations (including figure design), and performed the validation of the findings by cross-checking the literature and data. TW reviewed and edited the manuscript, contributed to the conceptualization of the study, and assisted with the investigation by contributing to literature review and analysis. ZLG reviewed and edited the manuscript, supervised the project, acquired funding for the study, provided resources (including access to databases, literature or other study materials), and was responsible for project administration (e.g., coordinating contributions from all authors and ensuring project timelines were met). Data authentication is not applicable. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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