

Wnt signaling arranges the fate of lipid metabolism: The role of gut microbes

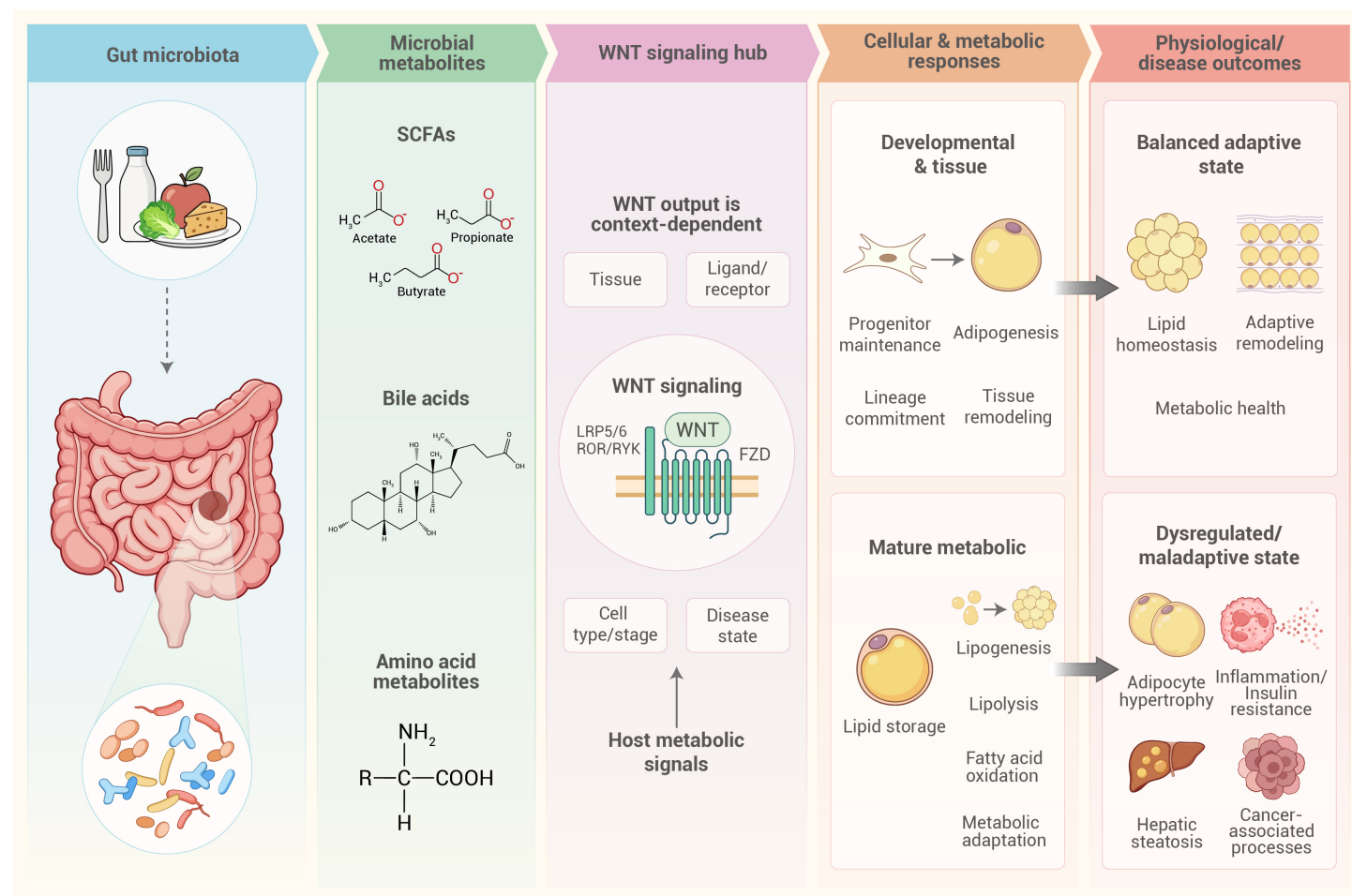
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Wnt signaling has dual roles in fat-cell development and metabolism.
- Metabolites from gut microbes can shift this balance, linking microbes to fat metabolism and tissue health.
- Gut microbes, their metabolites, and Wnt signaling offer potential therapeutic targets.

Wnt signaling arranges the fate of lipid metabolism: The role of gut microbes

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Disrupted lipid metabolism contributes to metabolic diseases and cancer. Gut microbes and their metabolites influence lipid absorption, synthesis, storage, and oxidation, while the Wnt signaling pathway is not only associated with lipid metabolism as a downstream metabolic pathway, but also serves as a regulatory system linking adipocyte lineage determination, tissue remodeling, and specific metabolic functions in mature adipocytes. How these components interact to form a gut microbes–metabolites–Wnt signaling axis, however, remains incompletely understood. Thus, this review focuses on the structure and physiological functions of Wnt, the association between Wnt signaling and host lipid metabolism. This review then examines how bile acids, amino acid metabolites, and short-chain fatty acids intersect with Wnt-related pathways across intestinal, hepatic, adipose, and cancer models. It further discusses the targeting of the gut microbes–metabolites–Wnt signaling axis for treatment, and explored the application prospects and challenges of gut microbes and their metabolites in the prevention and treatment of metabolic diseases and cancer.

INTRODUCTION

Disruption of lipid homeostasis contributes to obesity, type 2 diabetes, and metabolic dysfunction-associated steatotic liver disease (MASLD; formerly NAFLD).¹ Gut microbes influence lipid absorption, synthesis, storage, and catabolism through bioactive metabolites.² However, the host signaling mechanisms that translate inputs from gut microbes into changes in adipose-cell composition and tissue function remain incompletely resolved. Changes in adipose lipid phenotypes involve two interrelated levels of regulation: lipid synthesis, storage, and mobilization in mature adipocytes, and progenitor recruitment and adipogenic differentiation, which determine adipocyte number and tissue composition.^{3–4} This dual requirement provides the rationale for focusing on Wnt signaling, because Wnt operates across both developmental and metabolic levels of adipose regulation. In mesenchymal and adipose progenitors, canonical Wnt/ β -catenin signaling controls progenitor maintenance, lineage commitment, and adipogenic differentiation by restraining the peroxisome proliferator-activated receptor γ (PPAR γ)–CCAAT/enhancer-binding protein α (C/EBP α) transcriptional program.^{3–5} Wnt signaling also contributes to adipose-progenitor proliferation, depot remodeling, and systemic metabolic phenotypes. Wnt secretion from paired related homeobox 1 (Prrx1⁺) progenitors is also required for progenitor proliferation and adipose tissue maintenance, linking lineage control to stem-cell homeostasis and tissue remodeling.⁶ Consistently, progenitor-specific β -catenin activation produces depot-dependent adipose remodeling and systemic metabolic effects.⁷ Wnt signaling remains operative after adipocyte differentiation. Evidence summarized in mature adipocytes indicates that Wnt/WLS-dependent signaling also participates in lipogenic programs, extending its role from cell-fate determination to lipid storage and metabolic function.⁸ Evidence that metabolites from gut microbes modulate host lipid handling and that Wnt functions differ across adipocyte developmental states provides the biological basis for evaluating their intersection. Therefore, Wnt is examined in this review as a context-dependent candidate integrative node linking microbial inputs with adipocyte lineage decisions, adipose-tissue remodeling, and mature lipid metabolism. This prioritization does not imply that Wnt is the sole or universally dominant mediator of metabolic effects mediated by gut microbes.

Recent reviews have addressed adjacent aspects of this field but were

organized around different central questions. Liu summarized how metabolites from gut microbes and multiple host pathways, including Wnt/ β -catenin signaling, regulate fat deposition.⁹ Hembra-Waduge et al. focused on Wnt/Wingless- and Hox-dependent transcriptional regulation of lipid metabolism, whereas Sanam et al. surveyed crosstalk between the host and gut microbes across a broad range of signaling pathways and disease contexts.^{10–11} These studies established the importance of each component, but did not provide a comprehensive overview of the gut microbes–Wnt–lipid metabolism axis relationship based on limiting factors such as Wnt specificity, ligand diversity, and cell developmental state. This review compares selected Wnt ligands in terms of their structural features, receptor context, and canonical or non-canonical signaling outputs. It distinguishes progenitor cells, preadipocytes, and mature adipocytes to interpret Wnt-regulated lipid phenotypes from a developmental perspective and discusses the interplay between metabolites derived from gut microbes and Wnt-regulated host metabolism. Finally, it evaluates the limitations of interventions targeting gut microbes, metabolites, and Wnt, thereby establishing a unified Wnt-centered analytical framework. Direct causal evidence is distinguished from associative evidence throughout, because the complete gut microbes–Wnt–lipid metabolism axis has not yet been established.

WNT STRUCTURE

In mammals, the Wnt family comprises 19 evolutionarily conserved, cysteine-rich secreted glycoproteins that are synthesized with an N-terminal signal peptide directing them into the endoplasmic reticulum (ER).^{12–13} Available Wnt structures reveal a conserved two-domain fold stabilized by multiple intramolecular disulfide bonds, although the precise number and positions of cysteine residues and surface loops vary among individual ligands.^{14–15} During maturation in the ER, Wnt ligands undergo porcine O-acyltransferase (PORCN)-catalyzed O-palmitoleoylation at a conserved serine residue; this lipid modification is required for efficient loading onto Wntless (WLS), secretion, and productive engagement with Frizzled (FZD) receptors.^{14,16} N-linked glycosylation is also common among Wnt proteins and generally contributes to protein folding and secretion, although the number of glycosylation sites and their functional importance vary among ligands.^{13,17} Following lipidation, Wnt ligands bind WLS in the ER and are transported through the secretory pathway to the plasma membrane, with a hydrophobic cavity in WLS accommodating the attached palmitoleate group.^{18–19} After release, Wnt proteins act through autocrine or paracrine mechanisms and bind the extracellular cysteine-rich domains of FZD receptors, frequently in cooperation with ligand- and tissue-specific co-receptors.^{12,14} Thus, Wnt proteins share a conserved framework of disulfide-stabilized folding, PORCN-dependent lipidation, WLS-mediated trafficking, and FZD-centered receptor recognition. However, this common molecular framework does not produce a uniform signaling response, because differences in ligand sequence, receptor and co-receptor composition, cell type, and physiological state determine whether β -catenin-dependent or β -catenin-independent signaling outputs predominate.^{20–22} Among these Wnt protein family members, WNT1, WNT3A, WNT5A, WNT7A/B, and WNT10A have received extensive research attention (Figure 1). Table 1 delineates the functions of these Wnt proteins.

WNT1

WNT1 is synthesized as a 370-amino-acid precursor containing an N-

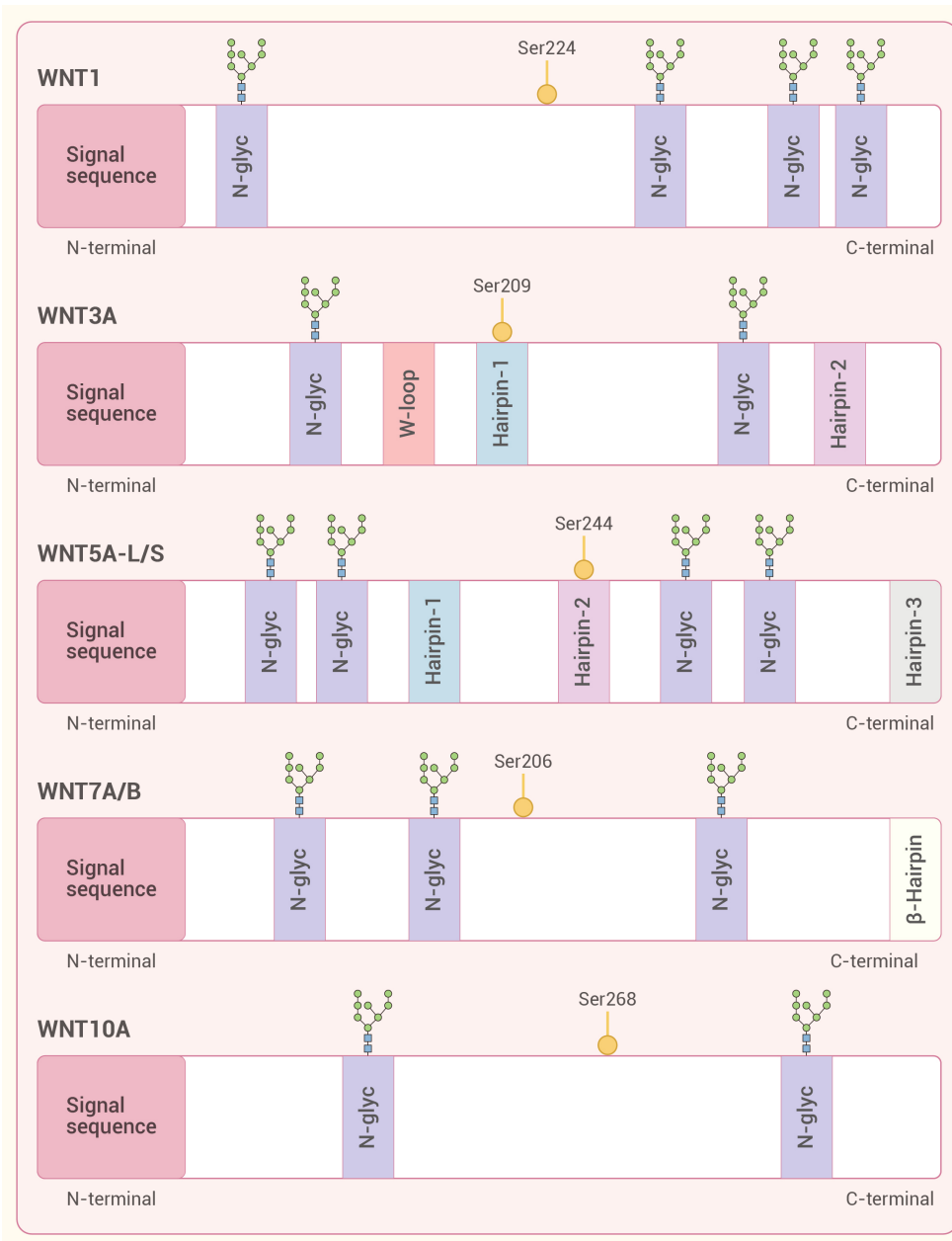


Figure 1. Structural features specific to representative Wnt proteins are outlined. Particular emphasis is placed on the ligand-specific characteristics of WNT1, WNT3A, WNT5A, WNT7A/B, and WNT10A.

sis of the WLS–WNT3A complex showed that WNT3A contains seven α -helices and six β -strands organized into N-terminal and C-terminal domains.¹⁹ Its N-terminal region contains a short 3_{10} helix formed by residues 22–26, while conserved disulfide bonds contribute to the stabilization of the overall conformation.^{19,27} Hairpin-1, Hairpin-2, and the W-loop constitute three representative surface elements of WNT3A. Hairpin-1 carries the conserved palmitoleoylated Ser209 residue, whereas Hairpin-2 and the W-loop contain the representative residues Trp333 and Trp150, respectively.^{19,28} These loop and hairpin regions display conformational flexibility in different protein-bound states.¹⁹ After PORCN-dependent lipidation and WLS-mediated secretion, WNT3A commonly engages FZD–LRP5/6 receptor complexes and strongly activates β -catenin-dependent transcription.²¹ WNT3A is therefore widely used as a representative canonical Wnt ligand in experimental systems. WNT3A has essential functions during embryonic development. *Wnt3a*-deficient mice exhibited impaired somite formation, posterior body-axis development, and tailbud organization, indicating that WNT3A supports mesodermal patterning and posterior progenitor maintenance.²⁹ Purified WNT3A also supported the proliferation or maintenance of selected stem and progenitor populations under defined culture conditions.³⁰ In mesenchymal progenitors and preadipocyte models, WNT3A-associated β -catenin activation suppresses the PPAR γ –C/EBP α program and restricts terminal adipogenic differentiation.^{5,31} This anti-adipogenic effect is most consistently observed before terminal differentiation. It therefore primarily reflects regulation of cell fate rather than direct control of lipid turnover in mature adipocytes.

terminal signal peptide.²³ PORCN-dependent O-acylation of WNT1 occurs at the conserved Ser224 residue, and the region spanning residues 214–234 is recognized and modified by PORCN.²³ WNT1 activates β -catenin-dependent signaling through FZD–LRP5/6 receptor complexes.²¹ This receptor configuration stabilizes β -catenin and promotes T-cell factor/lymphoid enhancer factor-dependent transcription.²¹ WNT1 has well-established functions in neural development and skeletal homeostasis. Targeted disruption of murine *Wnt1* caused severe abnormalities in the midbrain and cerebellum, demonstrating its requirement for regional brain patterning and neural progenitor development.²⁴ In humans, pathogenic *WNT1* variants are associated with early-onset osteoporosis and osteogenesis imperfecta, supporting an additional role in bone formation and skeletal integrity.²⁵ These findings indicate that WNT1 regulates cell-fate decisions in both neural and mesenchymal tissues. WNT1 can also influence adipocyte-lineage commitment. Experimental *Wnt1* expression maintained preadipocytes in an undifferentiated state and prevented induction of PPAR γ and C/EBP α .³ These findings support an anti-adipogenic role for WNT1 during precursor-cell differentiation.

WNT3A

After cleavage of its signal peptide, mature WNT3A contains 334 amino acids and has a molecular mass of approximately 44 kDa.²⁶ Structural analy-

WNT5A

Alternative transcription initiation generates two WNT5A protein isoforms with distinct N-terminal sequences, designated WNT5A-L and WNT5A-S.³² The WNT5A-L precursor contains 380 amino acids and produces a 337-amino-acid mature protein, whereas the WNT5A-S precursor contains 365 amino acids and produces a 319-amino-acid mature protein.³² Despite their different N-terminal sequences, the two isoforms share a conserved cysteine-rich structural core stabilized by disulfide bonds.³³ The C-terminal β -hairpin region, designated hairpin-3, spans approximately residues 353–371 and is stabilized by three disulfide crosslinks, with Phe359 and Val365 representing conserved residues within this region.³⁴ Biochemical analysis of mouse WNT5A identified four N-linked glycosylation sites at Asn114, Asn120, Asn311, and Asn325 and reported palmitoylation at Cys104.¹⁷ More recent cryo-electron microscopy analysis of the human WNT5A–WLS complex directly resolved the conserved O-palmitoleoylated Ser244 at the tip of hairpin-2, which inserts into the hydrophobic cavity of WLS; the structure also showed that WNT5A engages WLS through three conserved hairpins and can adopt a dimeric arrangement in the WLS-bound state.³⁵ Following its secretion, WNT5A can engage several FZD receptors and receptor tyrosine kinase-like orphan receptors, particularly receptor tyrosine kinase-like orphan receptor 2 (ROR2).³⁶ ROR2-dependent WNT5A signaling activates c-Jun N-termi-

Table 1. Principal biological functions and metabolic relevance of representative Wnt ligands.

Wnt ligand	Principal biological functions	Lipid metabolic relevance
WNT1	Predominantly activates canonical FZD-LRP5/6-β-catenin signaling and regulates neural development, skeletal homeostasis, and mesenchymal cell-fate decisions.	Maintains preadipocytes in an undifferentiated state and suppresses induction of the adipogenic transcription factors PPARγ and C/EBPα.
WNT3A	A representative canonical Wnt ligand that supports embryonic axis formation and the maintenance or proliferation of selected stem and progenitor populations.	Activates β-catenin signaling in mesenchymal progenitors and preadipocytes, thereby suppressing the PPARγ-C/EBPα program and restricting terminal adipogenic differentiation.
WNT5A	Preferentially activates ROR/FZD-dependent PCP, JNK, or Ca ²⁺ -related signaling, although its effects on β-catenin signaling depend on receptor and cellular context. It regulates morphogenesis, cell migration, inflammation, and tissue remodeling.	Promotes adipose-tissue inflammation and insulin resistance through the SFRP5-WNT5A-JNK axis, while its effects on adipogenic differentiation vary among cellular contexts.
WNT7A WNT7B	Use tissue-specific receptor complexes to regulate limb patterning, skeletal-muscle regeneration, central nervous system angiogenesis, blood-brain barrier formation, and pulmonary development.	Direct evidence linking WNT7A/WNT7B to adipocyte differentiation or lipid metabolism remains limited.
WNT10A	Predominantly activates β-catenin-dependent signaling and regulates ectodermal development and mesenchymal lineage allocation.	Stabilizes β-catenin, suppresses the PPARγ-C/EBPα adipogenic program, and shifts mesenchymal progenitor differentiation away from adipogenesis toward osteoblastogenesis.

nal kinase (JNK) and regulates cytoskeletal organization, polarity, and cell migration.³⁶ WNT5A can also activate Ca²⁺-associated signaling in selected neuronal contexts, where ROR2, phospholipase C, and intracellular Ca²⁺ mobilization contribute to downstream responses.³⁷ WNT5A signaling cannot be classified as exclusively non-canonical. Purified WNT5A activated or inhibited β-catenin–T-cell factor/lymphoid enhancer factor (TCF/LEF) signaling depending on the available receptor combination, demonstrating that receptor context can redirect its downstream output.²⁰ WNT5A therefore commonly engages planar cell polarity (PCP)-, JNK-, or Ca²⁺-related pathways, and can also modulate β-catenin signaling under specific cellular conditions.

WNT5A has broad functions in embryonic morphogenesis, cell migration, inflammation, and tissue remodeling. *Wnt5a*-deficient mice showed impaired extension of the limbs, face, tail, and several internal structures, supporting its role in directional tissue growth and coordinated morphogenesis.³⁸ Its effects on polarity and cytoskeletal organization also contribute to cell migration during development and tissue remodeling.³⁶ WNT5A is also implicated in obesity-associated metabolic dysfunction. The secreted frizzled-related protein 5 (SFRP5)–WNT5A–JNK axis has been linked to adipose-tissue inflammation and impaired glucose homeostasis in mouse models.³⁹ Genetic and functional studies further indicated that WNT5A-related non-canonical signaling promoted adipose inflammation and insulin resistance independently of substantial adipose-tissue expansion.⁴⁰ Increased non-canonical Wnt activity in human visceral adipose tissue has likewise been associated with local and systemic inflammatory markers.⁴¹ Its effects on adipogenic differentiation are not uniform. In skeletal-muscle fibro/adipogenic progenitors, WNT5A activated a GSK3β–β-catenin-related mechanism that restricted inappropriate adipogenic differentiation.⁴² Together, these findings highlight the context-dependent signaling characteristics of WNT5A.

WNT7

The WNT7 subgroup comprises two closely related paralogous ligands, WNT7A and WNT7B, rather than two isoforms of a single gene.²² Both proteins contain 349 amino acids and share approximately 77.1% amino-acid sequence identity.⁴³ WNT7B contains three predicted N-linked glycosylation sites in addition to the conserved cysteine-rich framework of Wnt proteins.⁴³ Structural studies of WNT7A have identified N-terminal and C-terminal domains, with the C-terminal region containing a conserved hairpin and a flexible linker, and its O-acylation occurs at the conserved Ser206 residue.⁴⁴ Lys40 and Ile60 represent distinctive residues on the WNT7A molecular surface.²² WNT7A and WNT7B share related structural features but use distinct receptor configurations in different tissues. In central nervous system endothelial cells, reversion-inducing cysteine-rich protein with Kazal motifs (RECK) and G protein-coupled receptor 124 (GPR124) form a tissue-restricted co-receptor system that enhances WNT7A/B signaling through

FZD–LRP5/6 complexes.^{45–46} In skeletal-muscle satellite cells, WNT7A can instead engage FZD7 and activate planar cell polarity-related signaling.⁴⁷ These examples demonstrate that receptor organization, rather than ligand identity alone, determines signaling output. WNT7A plays a role in limb pattern formation and skeletal muscle regeneration. Loss of *Wnt7a* disrupted dorsal limb identity and altered dorsoventral limb organization, demonstrating its requirement for embryonic spatial patterning.⁴⁸ In adult skeletal muscle, WNT7A–FZD7 signaling promoted the symmetric expansion of satellite stem cells through a planar cell polarity-related mechanism, thereby supporting regenerative capacity.⁴⁷ WNT7A and WNT7B also contribute to central nervous system angiogenesis and blood–brain barrier formation. Wnt-dependent β-catenin signaling was required for vascular development in the central nervous system but was less critical for angiogenesis in non-neural tissues.^{49,50} RECK and GPR124 selectively enhanced WNT7A/B signaling in this neurovascular context, providing a mechanism for tissue-specific ligand recognition.^{45–46} WNT7B additionally regulates pulmonary development. *Wnt7b* deficiency reduced lung mesenchymal proliferation and disrupted pulmonary vascular development, resulting in severe respiratory abnormalities in mice.⁵¹ Together, these findings highlight the tissue-specific roles of WNT7A and WNT7B in development and tissue regeneration.

WNT10A

Human and mouse WNT10A proteins each contain 417 amino acids, whereas zebrafish *Wnt10a* contains 442 amino acids.^{52–53} Human WNT10A contains an N-terminal signal peptide followed by a conserved Wnt core domain, and its O-acylation occurs at the conserved Ser268 residue.⁵² Sequence conservation and homology modeling suggest that WNT10A adopts the characteristic Wnt fold with disulfide-stabilized structural regions, although its detailed architecture has not been directly resolved experimentally.⁵³ This configuration was extrapolated from computational and experimentally determined structures of other Wnt–FZD complexes rather than from a directly resolved WNT10A–FZD structure.^{14,54–55} Following its conserved processing and secretion, WNT10A predominantly activates β-catenin-dependent signaling in mesenchymal lineage models.³ In mesenchymal precursor cells, the effects of WNT10A on lineage allocation were abolished when β-catenin signaling was disrupted, supporting a β-catenin-dependent mechanism.⁵⁶ WNT10A also influences mesenchymal progenitor-cell fate. In cell-based differentiation models, WNT10A stabilized β-catenin, suppressed the PPARγ–C/EBPα adipogenic program, and promoted osteoblastogenesis.⁵⁷ WNT6 and WNT10B produced similar anti-adipogenic and pro-osteogenic effects in the same experimental framework, indicating partially overlapping functions in mesenchymal lineage allocation.⁵⁶ These findings identify WNT10A as a β-catenin-dependent regulator that suppresses adipogenesis and promotes osteoblastogenesis.

Functions of representative Wnt proteins

Collectively, these representative Wnt ligands share a conserved role as secreted morphogens that translate local extracellular cues into changes in cell fate, progenitor maintenance, tissue patterning, and remodeling.^{12,21} WNT1, WNT3A, and WNT10A most consistently engage β -catenin-dependent programs and restrict adipogenic commitment in precursor cells.^{3,5,56} By contrast, WNT5A more commonly activates ROR or RYK/FZD-dependent PCP, JNK, or Ca^{2+} -related pathways and shows context-dependent effects on adipogenesis, inflammation, and insulin responsiveness.^{20,36,39} WNT7A and WNT7B use tissue-restricted receptor complexes to regulate neurovascular, skeletal-muscle, and pulmonary development, whereas direct evidence connecting these ligands to adipocyte lipid metabolism remains limited.^{45-47,51} Their shared molecular framework therefore supports cell-state regulation, whereas ligand-specific receptor usage and tissue context generate divergent biological outcomes.

WNT SIGNALING AND LIPID METABOLISM

Wnt signaling participates in metabolic regulation beyond its established functions in development and tissue homeostasis.²¹ Wnt-related pathways intersect with glucose and insulin homeostasis, nutrient sensing, and cellular energy metabolism, but their metabolic outputs vary across ligands, receptors, cell types, and physiological states.⁹ In the liver, recent mouse studies identified leucine-rich repeat-containing G protein-coupled receptor 4 (LGR4)–Wnt/ β -catenin/transcription factor 7-like 2 (TCF7L2) signaling and R-spondin 3 (RSPO3)-dependent metabolic zonation as regulators of gluconeogenesis, insulin sensitivity, and inter-organ metabolic communication.⁵⁸⁻⁵⁹ Spatial genomic analyses further indicated that hepatic TCF7L2 organizes zoned programs involving cholesterol, bile acid, and glutamine–glutamate metabolism, whereas disruption of these programs increased susceptibility to diet-induced fibrosis.⁶⁰ In pancreatic β cells, R-spondin 1 (RSPO1)-mediated Wnt activation promoted β -cell replication and neogenesis across experimental models, while the long noncoding RNA TUNAR fine-tuned Wnt signaling to regulate human β -cell proliferation.⁶¹⁻⁶² Wnt-related processes have also been associated with hepatic mitochondrial organization and endocrine fibroblast growth factor 21 signaling, linking nutrient sensing with cellular energy adaptation.⁶³⁻⁶⁴ These broader interactions provide the metabolic context in which Wnt regulates substrate allocation, lipid synthesis, storage, mobilization, and adipocyte function.

Wnt signaling regulates fatty acid synthesis, cholesterol homeostasis, and lipid storage and mobilization.⁶⁵ These effects are pathway specific. Canonical Wnt/ β -catenin signaling primarily establishes long-term, cell-specific metabolic phenotypes through transcriptional control of lipid-metabolic genes.⁶⁶ By contrast, non-canonical Wnt/PCP and Wnt/ Ca^{2+} pathways more often regulate rapid responses, including lipid-droplet dynamics and lipolysis, through cytoskeletal remodeling, membrane dynamics, and second-messenger signaling.^{8,67} Studies have shown that Wnt signaling maintains systemic lipid homeostasis by positively or negatively regulating key steps of lipid metabolism, and this regulatory role is evolutionarily conserved in *Drosophila* adipocytes as well as mammalian adipose tissue and liver.⁶⁸ The following sections describe the distinct mechanisms and pathophysiological significance of these two pathways in the regulation of lipid metabolism (Figure 2).

Canonical Wnt signaling

Canonical Wnt/ β -catenin signaling is controlled by β -catenin stability.⁶⁵ In the absence of a Wnt ligand, cytoplasmic β -catenin is constitutively targeted for degradation.⁶⁹ A destruction complex comprising Axin, adenomatous polyposis coli (APC), casein kinase 1 α (CK1 α), and glycogen synthase kinase 3 β (GSK-3 β) mediates this process.⁷⁰ Within the complex, CK1 α and GSK-3 β sequentially phosphorylate β -catenin, marking it for ubiquitination and proteasomal degradation.²¹ The pathway is activated when secreted Wnt ligands, including WNT3A and WNT1, bind a cell-surface receptor complex.⁷¹ This complex comprises a seven-transmembrane FZD receptor and the co-receptor, LRP5/6.⁷² Ligand binding recruits the cytoplasmic adaptor Dishevelled (DVL) and promotes LRP5/6 phosphorylation.⁷³ Phosphorylated LRP5/6 sequesters Axin at the plasma membrane and destabilizes the destruction complex.⁷² β -catenin phosphorylation and degradation then cease.⁷⁴ Stabilized β -catenin accumulates in the cytoplasm and translocates into the

nucleus.⁷⁵ There, it binds TCF/LEF family transcription factors and displaces corepressors such as Groucho.⁷⁶ The β -catenin-TCF complex then recruits co-activators and induces target genes involved in proliferation, differentiation, and metabolism, including MYC and CCND1.⁷⁷ Dysregulation of this pathway contributes to multiple diseases. Gain-of-function mutations in *CTNNB1* (encoding β -catenin) or loss-of-function mutations in tumor suppressors like *APC* lead to constitutive pathway activation and are recognized drivers of various cancers.⁷⁸ Conversely, impaired signaling, for instance through mutations in the co-receptor *LRP6*, has been linked to metabolic disorders such as MASLD, highlighting its critical role in metabolic homeostasis.⁷⁹ Thus, canonical Wnt signaling couples β -catenin stability to transcriptional regulation in development, metabolism, and disease.

Canonical Wnt signaling does not exert a uniform effect across adipocyte development because its biological output depends on cellular differentiation state.⁸ In mesenchymal progenitors and preadipocytes, WNT6, WNT10A, and WNT10B stabilized β -catenin and prevented induction of PPAR γ and C/EBP α , thereby restricting terminal adipogenic differentiation.^{3,5,56} In human adipose progenitors, transient canonical Wnt activation preserved an undifferentiated multipotent cell population under adipogenic pressure, further supporting a cell-fate maintenance function before terminal differentiation.⁴ During adipogenesis, endogenous Wnt signaling components were transiently repressed, whereas several pathway components were subsequently retained or re-expressed in mature adipocytes.^{5,80} Adipogenic differentiation concurrently established a PPAR γ - and C/EBP-dependent regulatory landscape that controlled genes involved in triglyceride synthesis, lipid storage, and carbohydrate metabolism.⁸¹⁻⁸² These epigenomic studies did not demonstrate that Wnt signaling directly caused this transcriptional transition; rather, they supported the interpretation that the developmental state and available transcription-factor network constrained how mature adipocytes responded to Wnt input.^{8,81-82} In mature adipocytes, endogenous Wnt secretion supported selected metabolic functions rather than adipogenesis itself.⁸³ Adipocyte-specific *Wls* deletion reduced free cytosolic β -catenin and Axin2 expression and coordinately decreased *Srebf1*, *Mlxip1*, *Acly*, *Acaca*, *Fasn*, and *stearoyl-CoA desaturase 1* (*Scd1*) expression, acetate incorporation into triacylglycerol, and monounsaturated fatty acid production.⁸³ The same intervention did not substantially alter insulin-stimulated glucose uptake, adrenergic lipolysis, or fatty acid oxidation in the cultured adipocyte model, indicating that adipocyte-derived Wnts exerted a selective rather than global pro-storage effect.⁸³ Other Wnt-related transcriptional components regulated different metabolic endpoints in mature adipocytes.⁸ Adipocyte-specific *Tcf7l2* deletion reduced triglyceride hydrolase expression and fasting-induced lipid mobilization and promoted adipocyte hypertrophy, increased adipose tissue mass, and impaired glucose metabolism under high-fat feeding.⁸⁴ Therefore, the apparently opposing effects of canonical Wnt signaling did not represent a simple reversal from inhibition of adipogenesis to promotion of lipid storage; instead, they reflected the distinction between cell-fate regulation in progenitors and regulation of selected metabolic functions within the transcriptional environment of differentiated adipocytes.

Non-canonical Wnt signaling

Non-canonical Wnt signaling comprises β -catenin-independent pathways that regulate cell polarity, migration, and tissue morphogenesis; its principal branches are Wnt/PCP and Wnt/ Ca^{2+} signaling.⁸⁵ WNT5A, WNT5B, and WNT11 are major ligands, but their outputs depend on receptor composition and cellular context.⁸⁶⁻⁸⁷ In the PCP pathway, Wnt–FZD activation directs DVL signaling through parallel DAAM1–RHOA and RAC1 branches.⁸⁸⁻⁸⁹ DVL forms a complex with DAAM1 and RHOA.⁸⁸ A distinct DVL–RAC1 complex forms independently of the RHOA branch.⁸⁹ The RAC1 branch, rather than the RHOA branch, mediates JNK activation.⁸⁹ PCP signaling thereby connects Wnt input to cytoskeletal organization, inflammatory responses, and vascular insulin resistance.⁹⁰ The Wnt/ Ca^{2+} pathway mobilizes intracellular Ca^{2+} through selected Wnt–FZD receptor combinations.⁹¹ The Wnt/ Ca^{2+} branch is a β -catenin-independent signaling route in which selected Wnt–FZD receptor combinations engage heterotrimeric G-protein-dependent phosphoinositide signaling and mobilize intracellular Ca^{2+} .⁹²⁻⁹³ In the classical model, phospholipase C (PLC) hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP₂) to generate inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol (DAG); IP₃

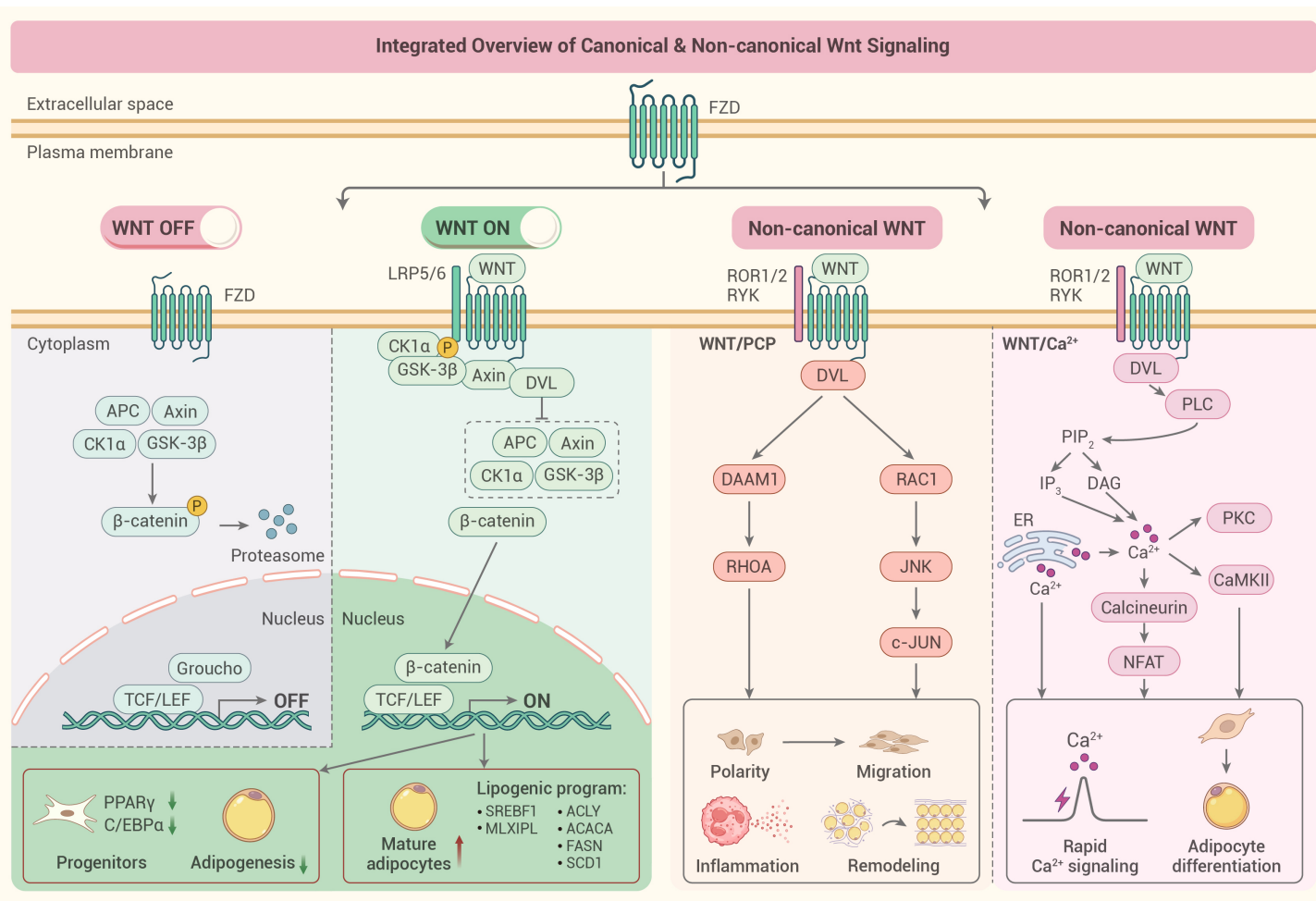


Figure 2. Canonical and non-canonical Wnt signaling pathways In the canonical pathway, the APC–Axin–CK1α–GSK-3β destruction complex phosphorylates and promotes the degradation of β-catenin in the absence of Wnt ligands. Wnt binding to FZD–LRP5/6 recruits DVL and Axin to the membrane, inhibits the destruction complex, and permits β-catenin accumulation and nuclear TCF/LEF-dependent transcription. This signaling restricts adipogenic commitment in progenitor cells but supports selected lipid-metabolic programs in mature adipocytes. In the non-canonical Wnt/PCP pathway, FZD and ROR/RYK receptors activate DVL-dependent DAAM1–RHOA and Rac1–JNK–c-JUN signaling to regulate cytoskeletal organization, polarity, migration, inflammation, and tissue remodeling. In the Wnt/Ca²⁺ pathway, activation of PLC generates IP₃ and DAG, leading to intracellular Ca²⁺ release and activation of PKC, CaMKII, and other Ca²⁺-responsive effectors.

promotes Ca²⁺ release from intracellular stores, whereas DAG together with Ca²⁺ activates protein kinase C (PKC).^{92–94} The increase in cytosolic Ca²⁺ further activates Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) and the phosphatase calcineurin.⁹³ Calcineurin dephosphorylates nuclear factor of activated T cells (NFAT), promoting its nuclear translocation and transcriptional activity.⁹¹ Together, the PCP and Ca²⁺ branches couple WNT–receptor activation to cytoskeletal remodeling, transcriptional regulation, and crosstalk with canonical Wnt signaling.

Non-canonical Wnt signaling contributes to adipocyte differentiation.⁴¹ During osteogenic versus adipogenic lineage commitment in multipotent mesenchymal stem cells (MSCs), WNT5A inhibited adipogenic differentiation and preserved osteogenic potential by activating the non-canonical Wnt/JNK/c-Jun axis, upregulating osteogenic genes, and suppressing PPARγ and SREBP1c.⁹⁵ Accordingly, downregulation of WNT5A signaling is required for commitment of MSCs toward preadipocyte lineages.⁹⁶ By contrast, WNT5A, WNT5B, and WNT4 can exert pro-adipogenic effects during preadipocyte differentiation.⁹⁷ WNT5B acts as a potent pro-adipogenic factor that directly upregulates the expression of *PPARγ* and *FABP4* while effectively repressing β-catenin nuclear translocation.⁹⁸ WNT5A promotes adipogenic differentiation by destabilizing β-catenin and acts synergistically with WNT5B.⁹⁹ In 3T3-L1 preadipocytes, WNT4 and WNT5A promoted early adipocyte differentiation, with WNT4 implicated in PKC-associated signaling.⁹⁹ In obese individuals, WNT5A and ROR1/2 expression is increased in visceral adipose tissue.¹⁰⁰ WNT5A–ROR signaling activates JNK, impairs tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1), disrupts adipose insulin signaling, and suppresses endothelial nitric oxide synthase

activity, thereby contributing to vascular insulin resistance.¹⁰¹ Elevated WNT5A expression also inhibits preadipocyte differentiation and adipocyte hyperplasia, promoting hypertrophy and dysfunction through a mechanism that appears independent of MAPK signaling.¹⁰² In models of metabolic dysfunction-associated steatohepatitis (MASH; formerly NASH), WNT5A and WNT11 signaling through ROR2 accelerated hepatic glucose oxidation and increased the supply of acetyl-CoA and NADPH for de novo lipogenesis.¹⁰³ These changes exacerbated hepatic lipid accumulation, inflammation, and oxidative stress, promoting progression from simple steatosis to MASH.¹⁰³ Finally, factors secreted under obesogenic conditions, including WNT5A, WNT5B, and SFRPs, induce the upregulation and nuclear translocation of the ROR2 receptor in premalignant pancreatic cancer cells, activating non-canonical pathways and promoting epithelial-mesenchymal transition (EMT), proliferation, and invasion, thus linking obesity to an elevated pancreatic cancer risk.¹⁰⁴ Collectively, non-canonical Wnt signaling does not exert a uniform effect on adipogenesis or metabolic homeostasis. Its output instead depends on ligand–receptor context, cellular differentiation stage, and tissue environment.

METABOLITES FROM GUT MICROBES, WNT SIGNALING, AND LIPID METABOLISM

Wnt signaling is regulated by host-derived inputs acting at multiple levels of the pathway. In mouse liver and primary hepatocytes, insulin activates phosphoinositide 3-kinase–mechanistic target of rapamycin complex 1 (mTORC1)-dependent lipogenesis and induces SCD1, which supplies palmitoleate for PORCN-mediated Wnt acylation, thereby increasing hepatic Wnt/β-

catenin activity.¹⁰⁵ This mechanism indicates that host nutritional status can regulate Wnt signaling during ligand maturation, before the ligand engages its receptor. Host tissues also secrete extracellular Wnt modulators. Adipocyte-derived SFRP5 antagonizes WNT5A–JNK signaling and limits obesity-associated adipose inflammation and insulin resistance.³⁹ Liver-secreted NOTUM inhibits Wnt signaling and, in male mice, promotes adipose thermogenic capacity and protects against diet-induced obesity.¹⁰⁶ These findings indicate that extracellular Wnt inhibition does not produce a uniform metabolic response; its effects depend on the Wnt ligand, target tissue, and downstream signaling context. Sclerostin provides a further example of inter-organ regulation through its interaction with adipocyte LRP4, although the extent to which its effects on lipid and glucose metabolism depend specifically on Wnt inhibition remains incompletely resolved.¹⁰⁷ These host-derived inputs establish the signaling context in which metabolites produced or modified by gut microbes act. Host- and gut microbe-derived regulation should therefore be viewed as interacting layers rather than independent categories. Host physiology, including intestinal transit time and luminal pH, can shape microbial composition and metabolite production, thereby modifying the metabolic environment in which host signaling pathways operate.¹⁰⁸ Conversely, microbial enzymes diversify host-synthesized metabolites into chemically distinct signaling molecules with tissue- and receptor-dependent effects.¹⁰⁹ Bile acids (BAs) provide a representative example of this sequential host–microbial co-metabolism. Primary BAs are synthesized from cholesterol in hepatocytes, conjugated, and secreted into bile, whereas gut microbes subsequently deconjugate and transform these host-derived molecules into a secondary bile acid pool.¹¹⁰ Some microbial bile acid products can undergo additional biotransformation by host tissues, thereby illustrating the bidirectional nature of bile acid metabolism.¹¹⁰ Accordingly, the following subsections consider BAs as host-synthesized signaling molecules modified by gut microbes before examining amino acid metabolites, short-chain fatty acids, and the context-dependent metabolic consequences of altered Wnt signaling (Figure 3).

BAs and Wnt signaling

BAs are host-synthesized and microbiota-modified signaling molecules.^{111–112} Primary BAs are synthesized in hepatocytes, conjugated, and secreted into bile, gut microbes then modify them through deconjugation, dehydroxylation, oxidation, and epimerization.¹¹³ These transformations reshape the composition and receptor activity of the BA pool, thereby influencing host metabolic signaling through receptors such as the farnesoid X receptor (FXR).^{114–115} Increasing evidence indicates that BA metabolism and Wnt signaling are reciprocally regulated. In the liver, β -catenin contributes to BA synthesis by inducing CYP7A1 and CYP27A1, two key biosynthesis enzymes.¹¹⁶ Hepatocyte-specific β -catenin deletion reduced BA-synthesizing enzymes and increased hepatic cholesterol and BA accumulation in mice, thereby increasing susceptibility to diet-induced steatohepatitis.¹¹⁷ These findings indicate that hepatic β -catenin contributes to BA and cholesterol homeostasis under metabolic stress.¹¹⁷ β -Catenin also participates in reciprocal crosstalk with FXR through direct physical interactions.¹¹⁸ In a murine model of cholestasis, β -catenin acted as a corepressor of FXR by retaining it in the cytoplasm and inhibiting its nuclear translocation, thereby maintaining hepatic BA synthetic flux.¹¹⁹

Evidence from intestinal models further links BAs modified by gut microbes to Wnt signaling. High-fat feeding increased the expression of RSPO3 and LGR4/5, as well as β -catenin-associated epithelial proliferation, in the colons of conventionally raised rodents.¹²⁰ These responses were attenuated by antibiotic treatment, BA sequestration, or germ-free conditions, implicating secondary BAs produced through metabolism by gut microbes in this process.¹²⁰ In colorectal cancer models, activation of FXR by chenodeoxycholic acid (CDCA) induced the expression of the transcriptional corepressor TLE3 and inhibited Wnt/ β -catenin signaling activity.¹²¹ Conversely, the intestinal bacterium *Lactobacillus intestinalis* converted CDCA into ursodeoxycholic acid (UDCA), which acted as an FXR antagonist and relieved FXR-mediated inhibition of Wnt signaling.¹²² This effect restored intestinal stem cell function and established an *L. intestinalis*–UDCA–FXR–Wnt axis in the regulation of intestinal stem cells.¹²²

Beyond direct Wnt-related effects, intestinal FXR activation initiates an

endocrine response by inducing human fibroblast growth factor 19 (FGF19) and its murine ortholog FGF15, thereby extending the effects of bile acid metabolism by gut microbes beyond the intestine.^{123–125} FGF19 enters the enterohepatic signaling axis and suppresses hepatic BA and cholesterol synthesis through the FGFR4– β -Klotho pathway while promoting fatty acid oxidation.¹²⁶ These effects reduce hepatic steatosis, improve insulin sensitivity, and decrease body weight in obesity models. The Wnt-regulated transcription factor TCF7L2 provides an additional connection between endocrine signaling and lipid metabolism. In mice, TCF7L2 transcriptionally upregulated intestinal FGF15 expression, whereas intestinal *Tcf7l2* deletion decreased ileal FGF15, increased circulating BA concentrations, and disrupted hepatic triglyceride homeostasis.¹²⁷ Randomized trials in nonalcoholic steatohepatitis have evaluated FGF19 analogues, providing translational evidence for targeting the FGF19 pathway but not for a specifically Wnt-dependent therapeutic effect.¹²⁸ Collectively, remodeling of the BA pool by gut microbes may influence host lipid metabolism through interconnected FXR- and Wnt-related signaling, including the intestinal FXR–FGF15/19 endocrine axis.

Amino acids and Wnt signaling

Gut microbes convert dietary and host-derived amino acids into bioactive metabolites that influence epithelial, immune, and metabolic signaling.¹²⁹ Specific bacterial taxa can metabolize tryptophan into tryptamine, indole-3-aldehyde, indole-3-propionic acid, and other indole derivatives.^{130–131} Members of the genus *Pseudomonas*, particularly *P. aeruginosa*, can catabolize tryptophan through a bacterial kynurenine–anthranilate pathway and produce metabolites including kynurenine, kynurenic acid, and 3-hydroxykynurenine.^{132–133} The aryl hydrocarbon receptor (AhR) represents a mechanistic node linking tryptophan-derived metabolites to the regulation of intestinal Wnt signaling.¹³⁴ In murine intestinal epithelial cells, AhR induced the expression of the negative Wnt regulators *RNF43* and *ZNRF3*, thereby restricting excessive stem cell proliferation and maintaining epithelial barrier integrity.¹³⁵ In colorectal cancer models, *Akkermansia muciniphila* altered tryptophan metabolism and suppressed AhR/ β -catenin-associated tumor progression.¹³⁶ Conversely, in colorectal cancer cells, APC loss upregulated *TDO2* expression through the TCF4/ β -catenin pathway, thereby accelerating the conversion of tryptophan into kynurenine.¹³⁷ This finding indicated that Wnt activation can also act upstream of kynurenine metabolism. Whereas the preceding evidence positions Wnt within intestinal tryptophan signaling, kynurenine extends this interaction to systemic lipid metabolism. In mice, adipocyte-derived kynurenine activated the AhR/STAT3/IL-6 pathway, disrupted adipocyte lipid homeostasis, and promoted obesity and insulin resistance.¹³⁸ These metabolic effects were abolished by adipocyte-specific AhR deletion.¹³⁸ More recently, *Christensenella massiliensis* was shown to convert kynurenine into kynurenic acid and to reduce hepatic steatosis, adipose accumulation, and metabolic dysfunction in high-fat diet-fed mice.¹³⁹

In addition, Wnt signaling output suppressed the expression of the core hepatic transcription factor *CEBPA* by promoting intracellular histidine and arginine metabolism.¹⁴⁰ Because CEBPA also participates in adipocyte maturation, Wnt-associated amino acid metabolic reprogramming may contribute to impaired adipogenic differentiation and ectopic lipid deposition.¹⁴¹ Branched-chain amino acids (BCAAs) represent a second metabolic node linking metabolism by gut microbes to Wnt signaling. The BCAA biosynthetic capacity of gut microbes, particularly that of *Prevotella copri* and *Bacteroides vulgatus*, was associated with insulin resistance and elevated circulating BCAA concentrations.¹⁴² BCAAs such as leucine enter cells through the amino acid transporter SLC7A5, a direct downstream target of Wnt/ β -catenin signaling.¹⁴³ Aberrant Wnt activation markedly upregulated SLC7A5 and promoting intracellular BCAA accumulation.¹⁴⁴ Elevated intracellular BCAA activate mTORC1, which further stabilizes β -catenin by inhibiting GSK3 β , thereby establishing a positive feedback loop among Wnt signaling, SLC7A5, and mTORC1.^{145–146} Activated mTORC1 also phosphorylates and activates sterol regulatory element-binding protein 1 (SREBP1).¹⁴⁷ Nuclear SREBP1 then induces major lipogenic enzymes, including fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC), thereby promoting de novo lipogenesis.¹⁴⁸

Glutamine metabolism and its tricarboxylic acid cycle-derived metabolite α -ketoglutarate also participate in the regulation of Wnt signaling, although the available evidence remains largely restricted to cancer models.¹⁴⁹ MYC can

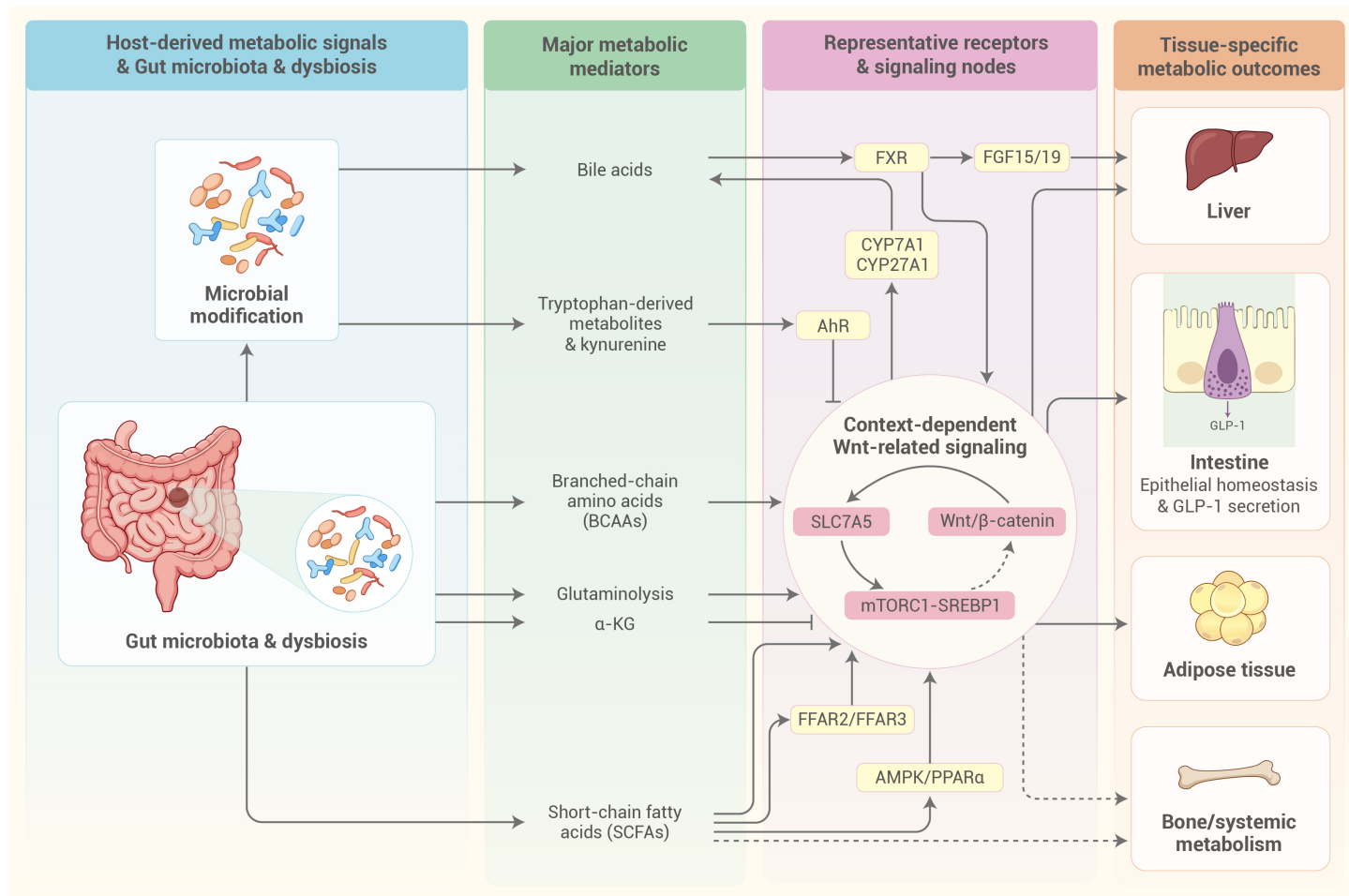


Figure 3. Context-dependent interactions among metabolites derived from gut microbes, Wnt-related signaling, and lipid metabolism Metabolites produced or modified by gut microbes, including BAs, amino acid metabolites, and short-chain fatty acids, modulate Wnt-related and parallel metabolic pathways in a tissue- and model-dependent manner, thereby affecting intestinal, hepatic, adipose, and systemic metabolic functions. Solid arrows indicate directly supported relationships, whereas dashed arrows indicate indirect or cross-model associations.

function both as a Wnt target and as an independent oncogenic transcription factor.¹⁵⁰⁻¹⁵¹ Under specific cellular conditions, MYC promotes the expression of amino acid transporters and glutaminases, thereby accelerating glutamine uptake and catabolism.¹⁵²⁻¹⁵³ In KRAS-mutant colorectal cancer cells, SLC25A22-dependent glutaminolysis reduced DNA demethylation and enhanced Wnt signaling activity, stemness, and drug resistance.¹⁵⁴ In APC-mutant colorectal cancer organoids, α-ketoglutarate supplementation promoted DNA and histone demethylation, attenuated Wnt target-gene expression, and induced cellular differentiation.¹⁴⁹ Activation of Wnt/β-catenin signaling also reprogrammed histidine and arginine metabolism by suppressing *CEBPA* and *FOXA1* in hepatocellular carcinoma cells.¹⁴⁰ Collectively, these findings support reciprocal regulatory interactions between Wnt signaling and amino acid metabolism.

Short-chain fatty acids and Wnt signaling

Short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, are produced through fermentation of dietary fiber by gut microbes.¹⁵⁵⁻¹⁵⁶ Among these metabolites, butyrate has emerged as the principal SCFA involved in the regulation of Wnt signaling and lipid metabolism, although accumulating evidence indicates that propionate and acetate also participate in these processes.¹⁵⁶ Evidence concerning butyrate illustrates the strong context dependence of gut microbes–Wnt interactions. In colorectal cancer cells with pre-existing dysregulation of canonical Wnt signaling, butyrate acts as a histone deacetylase inhibitor and can further increase β-catenin/TCF transcriptional activity.¹⁵⁷ However, this hyperactivation is associated with increased apoptosis rather than a generalized tumor-promoting response.¹⁵⁸⁻¹⁵⁹ In other colorectal cancer models, butyrate reduced β-catenin transcriptional activity by promoting its autophagy-dependent degradation, indicating that

even within tumor cells, the direction of Wnt regulation depends on the genetic background and the predominant downstream mechanism.¹⁶⁰ These direct-exposure studies should be distinguished from interventions targeting gut microbes that alter intestinal butyrate production together with other microbes and metabolic features. *Clostridium butyricum* inhibited Wnt/β-catenin signaling while simultaneously increasing cecal SCFA concentrations, activating SCFA receptors, and restructuring gut microbes in *Apc*-mutant mice; therefore, the observed phenotype cannot be attributed to butyrate alone.¹⁶¹ Conversely, dietary sodium butyrate was associated with increased Wnt/β-catenin-related signaling and improved intestinal development and barrier function in rabbits.¹⁶² In mice, butyrate expanded the regulatory T-cell population, which subsequently promoted *Wnt10b* expression in CD8⁺ T cells and stimulated bone formation.¹⁶³ These apparently opposing findings indicate that the effects of butyrate on Wnt signaling differ in direction across models. Although butyrate illustrates the context dependence of SCFA–Wnt interactions, other SCFAs can intersect with Wnt-related signaling through distinct receptor-mediated mechanisms. Propionate, produced by members of the phyla Bacteroidetes and Firmicutes, stimulates glucagon-like peptide-1 (GLP-1) secretion through free fatty acid receptor 2 (FFAR2; also known as GPR43) and FFAR3, as demonstrated in receptor-deficient mice and primary colonic cultures.¹⁶⁴ Consistent with this receptor-mediated effect, propionate activated the FFAR2–Wnt/β-catenin–TCF7L2 signaling axis in enteroendocrine cells and in a mouse model of gestational diabetes.¹⁶⁵ In adults with obesity, targeted colonic delivery of propionate increased postprandial peptide YY (PYY) and GLP-1 concentrations while limiting body-weight gain, intra-abdominal adipose accumulation, and hepatic lipid deposition.¹⁶⁶

Beyond enteroendocrine signaling, SCFAs also influence lipid metabolism in peripheral tissues through partly Wnt-independent mechanisms. In high-

fat diet-fed mice, SCFAs promoted a PPAR γ -dependent metabolic shift from lipid synthesis toward fatty acid oxidation and improved systemic energy metabolism.¹⁶⁷ GPR43 signaling in adipose tissue restricted insulin-dependent fat accumulation, whereas butyrate increased energy expenditure and improved insulin sensitivity in obese mice.^{168–169} A recent study showed that butyrate promoted the browning of white adipose tissue in mice with diet-induced obesity, accompanied by reduced HDAC9 activity.¹⁷⁰ Pasteurized *Akkermansia muciniphila* preparations also increased intestinal SCFA concentrations and alleviated adipose accumulation and hepatic steatosis, accompanied by alterations in GLP-1 and AMPK/PPAR- α signaling.¹⁷¹ At the cellular level, SCFAs increased lipid accumulation in differentiating 3T3-L1 cells, whereas dietary SCFA supplementation reduced adipose deposition and altered the expression of lipid metabolism-related genes in pigs.^{172–173} Collectively, SCFAs regulate lipid metabolism through Wnt-related, receptor-mediated, and peripheral metabolic pathways, although direct evidence for a complete gut microbes–SCFA–Wnt–lipid metabolism axis remains limited.

Adaptive versus maladaptive Wnt signaling

In mature adipocytes, endogenous Wnt secretion through WLS maintains selected lipogenic genes and protects against diet-induced metabolic dysfunction.⁸³ Similarly, adipocyte-specific deletion of the Wnt-related transcriptional factor *Tcf7l2* impaired fasting-induced lipid mobilization, promoted adipocyte hypertrophy, and worsened glucose metabolism.⁸⁴ These findings indicate that adequate Wnt-related signaling can support adipocyte function and metabolic homeostasis. By contrast, excessive or persistent Wnt signaling can become maladaptive. Enhanced paracrine RSP01–LGR4/Wnt signaling suppresses beige adipocyte thermogenesis and favors adiposity, whereas sustained non-canonical WNT5A–ROR signaling in visceral adipose tissue promotes inflammatory and insulin-resistant phenotypes.^{41,174} Thus, both insufficient and excessive Wnt activity may disrupt lipid homeostasis, although they act through different cell populations and metabolic programs. Studies of metabolites from gut microbes further demonstrate that the direction of Wnt regulation does not by itself determine the biological outcome. Butyrate-induced Wnt hyperactivation in colorectal cancer cells was associated with increased apoptosis, whereas *Clostridium butyricum* suppressed Wnt/ β -catenin signaling and inhibited intestinal tumor development in *Apc*-mutant mice.^{158,161} Conversely, dietary sodium butyrate increased Wnt-associated signaling while improving intestinal development and barrier function in rabbits.¹⁶² Therefore, Wnt activation can be protective or pathogenic, and Wnt inhibition may likewise be beneficial or harmful. Accordingly, pathological Wnt dysregulation should be distinguished from adaptive changes in Wnt activity. To distinguish mechanistic findings from cell-based studies, in vivo validation in animal models, and human translational evidence, Table 2 provides a structured qualitative appraisal of the reported interactions between gut microbes, Wnt signaling, and lipid metabolism. This structure was selected to identify the specific missing links within each proposed causal pathway. Rather than assigning a single overall evidence grade, the appraisal evaluates whether the individual components of the proposed pathway, including the microbial input, Wnt dependence, and lipid or metabolic outcome, have been directly established and whether these relationships have been demonstrated within the same experimental system. It therefore distinguishes evidence supporting individual segments of a proposed pathway from evidence demonstrating causal continuity across the entire pathway.

DISEASE RELEVANCE OF GUT MICROBES–WNT INTERACTIONS

Obesity is associated with altered diversity, taxonomic composition, and metabolic profiles of gut microbes. In a meta-analysis by Gong et al., individuals with obesity showed reduced microbial diversity, an increased Bacteroidetes-to-Firmicutes ratio, and several taxonomic and functional alterations.¹⁷⁵ *Akkermansia muciniphila* abundance is inversely associated with obesity and diabetes, and experimental evidence links this species to improved intestinal barrier function through Wnt-related signaling.^{176–177} Wnt signaling also contributes to adiposity through host mechanisms. *Rspo1* overexpression activated LGR4–Wnt/ β -catenin signaling, suppressed mitochondrial respiration and thermogenesis in beige adipocytes, and exacerbated adiposity.¹⁷⁴ *Lztf11* deficiency reduced Wnt/ β -catenin signaling and

increased lipid accumulation and systemic obesity in mice.¹⁷⁸ These studies identify gut microbes-associated and host Wnt-related features of obesity, but do not yet establish a unified gut microbes–Wnt causal pathway.

Obesity-related Wnt dysregulation is unlikely to exert uniform effects across adipose cell populations.⁴ Single-cell and spatial analyses have revealed substantial heterogeneity among adipose progenitors, stromal cells, and mature adipocytes, indicating that obesity involves altered cellular composition as well as lipid accumulation.^{179–180} In adipose progenitors, persistent canonical Wnt activity can restrict adipogenic commitment and reduce the capacity for hyperplastic expansion during chronic energy excess.^{4,181} Consistently, preserving adipose stem and progenitor cell expansion and differentiation improved glucose homeostasis in obese mice, supporting the metabolic importance of progenitor competence.¹⁸² By contrast, WLS- and TCF7L2-related signaling supports selected lipid-handling functions after adipocyte differentiation, and its disruption promotes adipocyte hypertrophy and impaired glucose metabolism.^{83–84} Thus, stage-specific Wnt imbalance may shift adipose expansion from metabolically adaptive hyperplasia toward hypertrophic dysfunction. Aberrant activation of specific Wnt-related pathways contributes to obesity through reduced energy expenditure and inflammatory adipose remodeling.^{40,183} RSP01–LGR4/Wnt signaling suppresses mitochondrial respiration and thermogenesis in beige adipocytes, whereas blockade of RSP01/2–LGR4 enhanced thermogenic activity and reduced adiposity in mouse models.^{174,184} In parallel, WNT5A-associated non-canonical signaling promotes adipose inflammation and impaired insulin responsiveness.^{40,41} Collectively, restricted adipose expandability, impaired thermogenesis, and WNT5A-related inflammation provide complementary mechanisms through which cell-specific Wnt dysregulation can contribute to obesity pathogenesis. Few studies have simultaneously linked a defined alteration in gut microbes to cell-specific Wnt dependency and obesity-related outcomes within the same experimental system. It also remains unclear whether altered Wnt activity initiates adipose dysfunction or represents a compensatory response to nutritional stress. Figure 4 summarizes how dysbiosis of gut microbes may contribute to obesity through Wnt-related mechanisms.

Beyond obesity, cancer represents another disease context in which signals from gut microbes intersect with Wnt signaling, with the strongest evidence currently available for colorectal cancer.¹⁸⁵ *Fusobacterium nucleatum* can activate E-cadherin/ β -catenin signaling through its FadA adhesin, whereas enterotoxigenic *Bacteroides fragilis* abundance has been associated with altered expression of Wnt-related genes in colorectal tumors.^{186–187} Fecal microbes from individuals with obesity also increased colorectal tumor burden and Wnt-related oncogenic signaling after transfer into mouse models, suggesting that obesity-associated dysbiosis may contribute to colorectal carcinogenesis.¹⁸⁸ Beyond the intestine, enterotoxigenic *Bacteroides fragilis* promoted breast tumor progression with β -catenin activation, whereas butyrate derived from gut microbes suppressed LRP5/ β -catenin signaling and cancer stemness in stress-associated breast cancer models.^{189–190} The host–microbial co-metabolite phenylacetylglutamine also inhibited prostate cancer progression by suppressing Wnt/ β -catenin signaling, although the gut microbes responsible for its production were not identified.¹⁹¹ Collectively, Wnt signaling may provide a context-dependent link between obesity-associated gut dysbiosis and cancer-related processes, although direct causal evidence for this gut microbe–Wnt relationship in humans remains limited. Genetic mouse models have been essential for distinguishing the developmental, cell-stage-specific, and tissue-specific functions of Wnt signaling (Table 3).

THERAPEUTIC IMPLICATIONS, CHALLENGES, AND SAFETY CONSIDERATIONS

The gut microbes–Wnt–lipid metabolism axis provides several potential intervention points in metabolic diseases and cancer. Evidence summarized in Sections 4 and 5 identifies three levels of intervention: modulation of gut microbes, administration or targeted delivery of defined metabolites, and direct regulation of Wnt signaling.^{8,192} Treatment efficacy and Wnt dependence need to be evaluated separately. In obesity, upstream strategies targeting gut microbes have shown preliminary metabolic efficacy, including probiotics, postbiotic preparations, and engineered bacteria.^{193–195} Pasteur-

Table 2. Structured qualitative appraisal of evidence linking metabolites from gut microbes, Wnt signaling, and lipid metabolism.

Metabolite or microbial input	Wnt-related mechanism	Lipid/metabolic outcome	Experimental context	Critical causal appraisal
Microbiota-modified secondary bile acid pool	Secondary BAs were implicated in increased colonic RSPO3 and LGR4/5 expression and β -catenin-associated epithelial proliferation.	A lipid endpoint was not measured in the Wnt-focused experiment.	Conventionally raised, antibiotic-treated and germ-free rodents; bile acid sequestration.	Interventional in vivo evidence supports a microbiota/bile acid→Wnt-related partial axis. The active bile acid species, requirement for Wnt, and downstream lipid consequences were not established in the same model.
CDCA and <i>Lactobacillus intestinalis</i> -derived UDCA	CDCA activated FXR–TLE3 and inhibited Wnt/ β -catenin; UDCA antagonized FXR and relieved FXR-mediated Wnt inhibition.	Restored intestinal stem-cell function; lipid metabolism was not assessed.	Colorectal cancer models and intestinal stem-cell models.	The <i>L. intestinalis</i> –UDCA–FXR–Wnt chain is a comparatively strong microbiota-to-Wnt mechanism, but it does not establish a microbiota–Wnt–lipid causal axis.
Bile acid synthesis and the FXR–FGF15/19 axis	Hepatic β -catenin regulated CYP7A1/CYP27A1 and interacted with FXR; intestinal TCF7L2 upregulated FGF15.	Altered bile acid and cholesterol synthesis, hepatic triglyceride homeostasis, fatty acid oxidation and steatosis-related phenotypes.	Hepatocyte-specific β -catenin knockout, murine cholestasis, intestinal Tcf7l2 deletion, obesity models and FGF19-analogue trials.	Host Wnt→bile acid/lipid regulation is supported, but the microbial input is absent from the same causal experiments. Clinical FGF19 evidence is pathway-specific, not Wnt-dependent.
Tryptophan-derived indoles	Indole-activated AhR–ARNT induced RNF43 and ZNRF3, thereby suppressing Wnt signaling; <i>Akkermansia muciniphila</i> reduced AhR/ β -catenin-associated tumor progression.	Barrier maintenance and tumor-related outcomes were reported; adipose or hepatic lipid outcomes were not tested.	Murine intestinal epithelial cells and colorectal cancer models.	Direct metabolite/AhR→Wnt regulation is supported in intestinal models. Its proposed effect on adipogenic differentiation or ectopic lipid deposition remains an extrapolation.
Kynurenine and kynurenic acid	APC loss activated TCF4/ β -catenin→TDO2 and increased kynurenine production. Wnt was not tested in the <i>C. massiliensis</i> obesity experiment.	Kynurenine activated adipocyte AhR/STAT3/IL-6 and promoted lipid dysregulation, obesity and insulin resistance; <i>C. massiliensis</i> reduced steatosis and adipose accumulation.	Colorectal cancer cells, adipocyte-specific AhR deletion and high-fat diet-fed mice.	Two causally informative segments exist, but in different models and with Wnt positioned upstream in one segment. Wnt necessity for the microbial intervention's lipid benefit remains untested.
Branched-chain amino acids (BCAAs)	Wnt/ β -catenin induced SLC7A5; intracellular BCAAs activated mTORC1, inhibited GSK3 β and stabilized β -catenin; mTORC1 activated SREBP1.	SREBP1 can induce FASN and ACC and promote de novo lipogenesis.	Human microbiome association plus mechanistic cell-based studies.	The proposed microbiota→BCAA→Wnt/mTORC1→lipogenesis route is assembled from separate studies. Microbial causality, Wnt necessity and lipid outcomes were not tested together.
Glutamine and α -ketoglutarate	SLC25A22-dependent glutaminolysis enhanced Wnt signaling; α -ketoglutarate promoted demethylation and reduced Wnt target-gene expression; Wnt also reprogrammed histidine/arginine metabolism via CEBPA and FOXA1 suppression.	Direct lipid outcomes were not assessed.	KRAS-mutant colorectal cancer cells, APC-mutant organoids and hepatocellular carcinoma cells.	This is evidence for reciprocal Wnt–amino acid regulation in cancer, not evidence for a gut microbiota–Wnt–lipid axis. Metabolic extrapolation should remain explicitly qualified.
Butyrate	Direction was context-dependent: HDAC inhibition hyperactivated pre-existing Wnt in colorectal cancer cells; <i>C. butyricum</i> or autophagy-dependent β -catenin degradation inhibited Wnt; sodium butyrate activated Wnt-associated signaling in rabbit intestine.	Separate studies reported increased energy expenditure and insulin sensitivity, reduced adiposity, and white-adipose browning; Wnt was generally not tested as the required mediator.	Colorectal cancer cells, Apc-mutant mice, rabbit intestine, immune models and diet-induced obesity models.	Strong evidence supports context-dependent butyrate→Wnt effects and independent butyrate→lipid effects. A closed-loop mechanism linking these effects in one model is lacking.
Propionate	Activated FFAR2/FFAR3-dependent incretin signaling and, in enteroendocrine cells and gestational-diabetes mice, the FFAR2–Wnt/ β -catenin–TCF7L2 axis.	Colonic propionate delivery increased PYY/GLP-1 and limited weight gain, intra-abdominal adiposity and hepatic lipid deposition in adults with overweight or obesity.	Primary colonic cultures, receptor-deficient mice, gestational-diabetes mice and a randomized human intervention.	The metabolite→Wnt and metabolite→lipid segments are experimentally supported, but mainly in different systems. The human metabolic effects were not shown to require Wnt signaling.
SCFA mixtures, acetate and SCFA-associated microbial interventions	Wnt signaling was not evaluated in the principal lipid-metabolism studies.	PPAR γ -dependent shift toward fatty acid oxidation, GPR43-mediated restriction of fat accumulation, AMPK/PPAR- α -associated improvement, and model-dependent changes in adipogenesis/adipose deposition.	High-fat diet-fed mice, 3T3-L1 adipocytes, pigs and microbial-intervention models.	These studies substantiate SCFA→lipid regulation but cannot support Wnt as the mediator. They should be presented as complementary, not closed-loop, evidence.

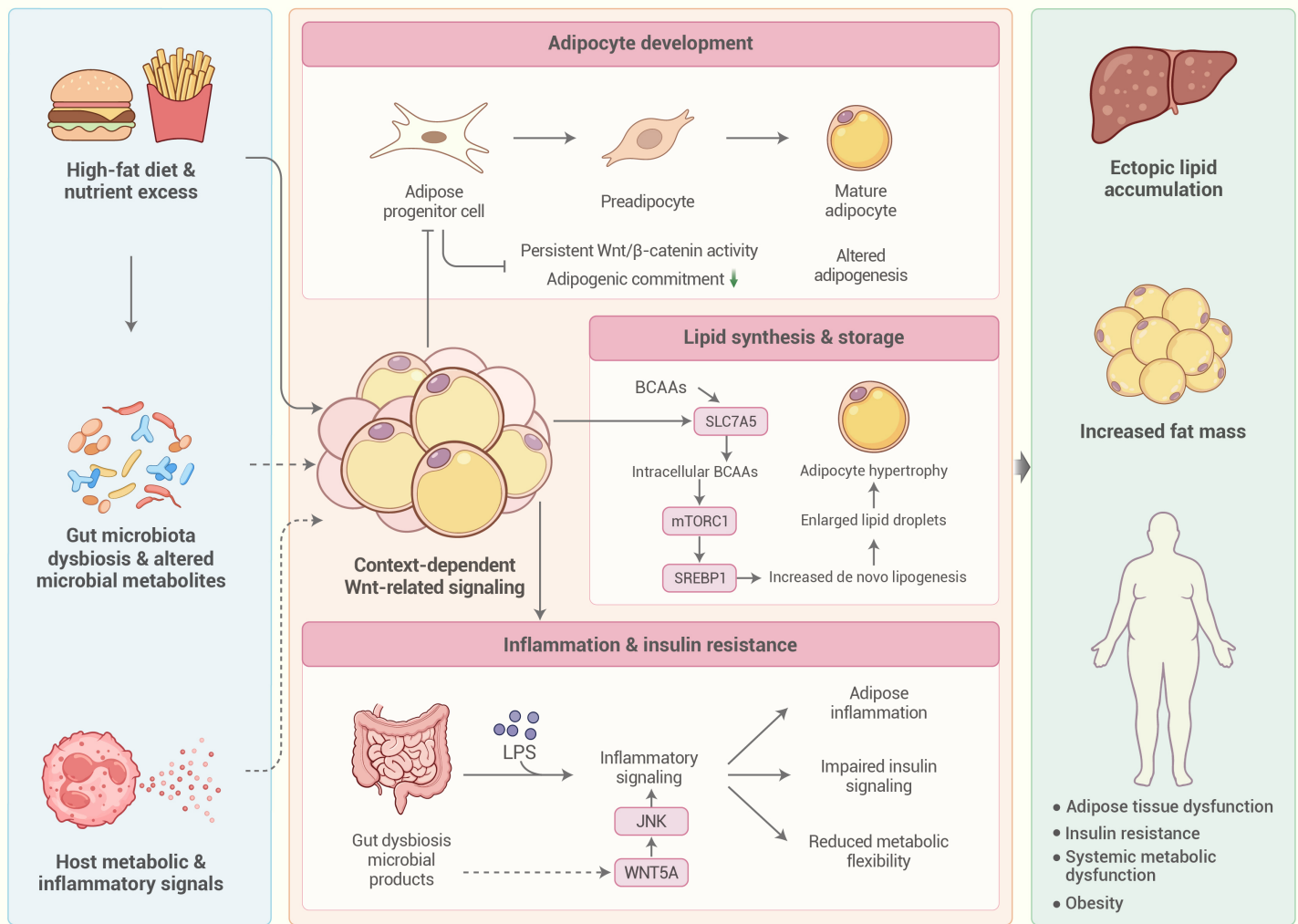


Figure 4. Wnt-related mechanisms contributing to obesity and adipose tissue dysfunction High-fat feeding, nutrient excess, dysbiosis of gut microbes, and altered metabolites reshape Wnt-associated and inflammatory signaling in adipose tissue. These changes disturb adipocyte differentiation, enhance SLC7A5–BCAA–mTORC1–SREBP1-associated lipid synthesis and storage, and promote adipose inflammation and insulin resistance, ultimately contributing to increased fat mass, adipose-tissue dysfunction, and obesity.

ized *Akkermansia muciniphila* improved selected metabolic outcomes in adults with overweight or obese, whereas engineered *Escherichia coli* Nissle 1917 reduced adiposity, insulin resistance, and hepatic steatosis in obese mice.^{194–195} Defined metabolite interventions allow narrower mechanistic attribution. Butyrate and other SCFAs improved insulin sensitivity, energy expenditure, and fatty acid oxidation in mice, whereas targeted colonic propionate delivery limited body-weight gain and adipose accumulation in overweight adults.^{166–167,169} Dietary α -ketoglutarate likewise reduced obesity and promoted beige adipogenesis in mice, although suppression of aberrant Wnt activity was demonstrated separately in cancer models.^{149,196} These findings support the therapeutic potential of interventions targeting gut microbes and their metabolites, but the extent to which Wnt signaling mediates their metabolic benefits remains uncertain. Direct Wnt modulation provides clearer evidence of pathway engagement but not necessarily greater therapeutic specificity.¹⁹⁷ Canonical Wnt signaling inhibits adipogenic commitment in progenitors, whereas selected Wnt-related components support lipid synthesis, mobilization, and metabolic homeostasis in mature adipocytes.^{8,83–84} Consistent with this rationale, increasing SFRP5 activity attenuated WNT5A-associated adipose inflammation and metabolic dysfunction in experimental obesity.³⁹ Wnt-directed therapies have also been investigated in cancer. In a phase I trial, the PORCN inhibitor WNT974 reduced AXIN2 expression in paired tissue samples, confirming pathway inhibition, but produced no objective responses and achieved disease stabilization in only 16% of patients.¹⁹⁸ α -Ketoglutarate also suppressed Wnt target-gene expression in APC-mutant colorectal cancer organoids, supporting modulation of aberrant Wnt output in a molec-

ularly defined setting.¹⁴⁹ These findings establish Wnt signaling as a therapeutically actionable pathway, but limited efficacy and safety concerns remain important limitations.

Although indirect or direct evidence indicated that gut microbes and their metabolites or other signaling molecules regulated Wnt targets, thereby effectively preventing and treating metabolic diseases and cancer, there are still challenges. The main challenge is the lack of direct evidence that Wnt signaling mediates the benefits of interventions targeting gut microbes or using metabolites. Metabolic improvement and Wnt regulation are often demonstrated in separate models, which does not establish a causal gut microbes–Wnt–lipid metabolism pathway. Future studies should manipulate a defined strain or metabolite, verify Wnt modulation in the target tissue, and test whether disruption abolishes the lipid-related benefit within the same experimental system.^{155,192} Second, Wnt output varies with ligand–receptor composition, target tissue, adipocyte developmental stage, disease state, signal intensity, and exposure duration.⁷¹ Because Wnt effects differ among progenitor cells, mature adipocytes, tissues, and tumor subtypes, global activation or inhibition is unlikely to produce consistent benefits.^{8,199} Metabolites from gut microbes are also pleiotropic and can regulate metabolic pathways independently of Wnt.^{155,192} Collectively, these challenges limit causal attribution and the development of predictable, context-specific interventions along the gut microbes–Wnt axis.

The safety of Wnt targets is an important factor that must take into consideration, which involved the systemic regulation of Wnt and may disrupt the homeostasis of normal tissues. Sustained Wnt activation may promote

Table 3. Representative genetic mouse models used to investigate Wnt signaling in lipid metabolism and related disease contexts.

Genetic model and manipulation	Target tissue / cell type	Wnt pathway alteration	Principal metabolic or disease phenotype	Finding and limitation
β -catenin activation in PPAR γ ⁺ adipose progenitors (PBCA; gain of function)	PPAR γ -expressing adipose progenitors	Persistent activation of canonical Wnt/ β -catenin signaling	Reduced fat mass and fibrotic replacement of subcutaneous adipose tissue; improved glucose homeostasis and increased insulin-independent muscle glucose uptake despite lipodystrophy.	Demonstrates stage- and depot-dependent control of progenitor fate and a fat-muscle endocrine effect. The strong developmental phenotype limits extrapolation to mature adipocytes; no microbial input was tested.
Adipocyte-specific <i>Wls</i> deletion (loss of function)	Mature adipocytes	Reduced adipocyte secretion of multiple Wnt ligands	<i>Wls</i> deletion in cultured adipocytes reduced lipogenic gene expression, de novo lipogenesis, and fatty-acid monounsaturations. In vivo effects were initially buffered on chow; after prolonged high-fat feeding, knockout mice showed reduced visceral adiposity and improved glucose homeostasis.	Defines adipocyte-derived Wnt secretion but also reveals stromal-vascular compensation and strong diet dependence. <i>Wls</i> deletion is not ligand-specific and does not model microbial regulation.
Adipocyte-specific <i>Ctnnb1</i> deletion (loss of function)	Mature adipocytes	Loss of canonical β -catenin signaling	Reduced Mlxip1/Srebf1-dependent lipogenic programs, de novo lipogenesis, and lipid desaturation. Compensation maintained tissue-wide signaling on chow, whereas prolonged high-fat feeding revealed resistance to obesity, adipocyte hypertrophy, and metabolic dysfunction.	Supports a direct role for β -catenin in mature-adipocyte lipid synthesis. Neighboring stromal cells compensate under basal conditions, so phenotype direction depends on diet duration and tissue context.
Adipocyte-specific <i>Tcf7l2</i> deletion (loss of function)	Mature adipocytes	Loss of a Wnt-associated transcriptional effector	Reduced triglyceride-hydrolase expression and fasting-induced lipid mobilization; adipocyte hypertrophy, increased adiposity, impaired glucose tolerance, and insulin resistance during high-fat feeding.	Shows that TCF7L2 supports mature-adipocyte lipid mobilization and metabolic adaptation. TCF7L2 activity is context dependent, so its deletion should not be interpreted as equivalent to global Wnt inhibition.
Global <i>Sfrp5</i> deletion (loss of function)	Systemic; adipose tissue is a major source of SFRP5	Reduced extracellular antagonism of WNT5A-JNK signaling	High-calorie feeding caused greater adipose inflammation, insulin resistance, glucose intolerance, and hepatic steatosis.	Supports a protective SFRP5-WNT5A balance in obesity. Whole-body deletion and the pleiotropic binding of secreted Wnt modulators limit tissue-specific and ligand-specific interpretation.
Myeloid-specific <i>Wnt5a</i> ablation and <i>Wnt5a</i> overexpression (loss- and gain-of-function models)	Myeloid cells, including macrophages	Bidirectional manipulation of non-canonical WNT5A-JNK signaling	<i>Wnt5a</i> ablation reduced adipose inflammation and improved insulin resistance in obesity; myeloid <i>Wnt5a</i> overexpression increased inflammation and impaired glucose homeostasis without materially changing fat mass or adipocyte size.	Provides complementary necessity and sufficiency evidence for immune-cell-derived WNT5A in metabolic inflammation. It primarily addresses inflammatory signaling rather than direct adipocyte lipid handling.
Liver-specific <i>Ctnnb1</i> deletion (Alb-Cre; loss of function)	Hepatocytes	Loss of hepatic β -catenin signaling	Defective bile-acid and cholesterol homeostasis, hepatic cholesterol and bile-acid accumulation, and increased susceptibility to diet-induced steatohepatitis.	Demonstrates a hepatocyte Wnt/ β -catenin contribution to bile-acid-lipid homeostasis. The model lacks a defined microbial manipulation, and β -catenin also has adhesion-related functions.
Inducible intestinal epithelial <i>Tcf7l2</i> deletion (Villin-CreERT2; loss of function)	Intestinal epithelium, especially ileal signaling	Reduced <i>Tcf7l2</i> -dependent <i>Fgf15</i> transcription	Reduced ileal <i>Fgf15</i> , increased circulating BAs, altered intestinal lipid uptake, and disrupted hepatic triglyceride homeostasis; complementary dosage models supported the same gut-liver axis.	Defines a Wnt-associated intestinal TCF7L2-FGF15 pathway controlling bile-acid and lipid homeostasis. It does not establish that microbial metabolites initiate the phenotype.
Osteoblast-specific <i>Wnt7b</i> overexpression (gain of function)	Osteoblasts / bone	Increased osteoblast-derived WNT7B signaling	Marked trabecular and cortical bone formation, reduced body-fat accumulation during prolonged high-fat feeding, and modest improvement of glucose tolerance in male mice.	Supports bone-adipose inter-organ effects of host Wnt signaling. The circulating mediator and direct Wnt dependence of the adipose phenotype remain unresolved; no microbial input was tested.
<i>Apc</i> Min/+ tumor-predisposition model combined with high-fat feeding and <i>Clostridium butyricum</i>	Intestinal epithelium / intestinal tumors	Constitutive canonical Wnt activation caused by <i>Apc</i> mutation; probiotic exposure reduced β -catenin-associated signaling	<i>C. butyricum</i> reduced high-fat-diet-associated intestinal tumor development, decreased tumor-cell proliferation, and increased apoptosis.	Provides a microbiota intervention in a genetically dysregulated Wnt background, but the model is oncologic rather than a direct lipid-metabolism model. It does not prove that Wnt suppression is required for the probiotic effect.

abnormal cell proliferation and oncogenic risk, whereas prolonged inhibition may impair intestinal epithelial renewal, tissue repair, and bone homeostasis.¹⁹⁹⁻²⁰¹ In the phase I trial of WNT974, dysgeusia occurred in 50% of patients, illustrating the adverse effects of systemic Wnt inhibition.¹⁹⁸ These risks may constrain the clinical application of prolonged or non-selective Wnt modulation. Interventions targeting gut microbes and metabolites also require specific safety evaluation. At the microbes level, therapeutic outcomes depend on strain-level variation, donor–recipient ecological compatibility, and disease indication; apparent restoration at the species level may conceal strain replacement, coexistence, or functional divergence.²⁰²⁻²⁰⁴ Metabolite interventions are similarly influenced by dose, route of exposure, tissue distribution, and host metabolic status. For example, although propionate is often considered metabolically beneficial, acute exposure can increase glucagon and fatty acid-binding protein 4 production and impair insulin action.²⁰⁵ Therapeutic development should therefore prioritize tissue-restricted, reversible, and time-limited interventions, with efficacy and safety evaluated in the same experimental system.

CONCLUSION

Crosstalk between gut microbes and Wnt signaling forms a context-dependent network linking microbial metabolites to host lipid metabolism and disease. BAs modified by gut microbes, amino acid metabolites, and SCFAs can alter Wnt-related signaling, whereas Wnt regulates adipocyte development, lipid storage and mobilization, thermogenesis, and inflammatory remodeling. Dysregulation of this network may contribute to obesity, insulin resistance, hepatic steatosis, and colorectal cancer progression. Evidence is strongest in obesity and colorectal cancer, but complete causal validation from a defined input from gut microbes through Wnt dependency to a metabolic phenotype remains limited. Future studies should combine defined microbes or metabolite interventions with tissue-specific Wnt manipulation, lipid phenotyping, and safety assessment. Direct Wnt-targeted therapies should focus on disease-relevant pathway components and restricted treatment windows to minimize systemic effects. Alternatively, defined strains, postbiotics, engineered bacteria, or targeted metabolite delivery may offer upstream approaches to modulate Wnt activity. Their therapeutic value will depend on demonstrating Wnt-dependent efficacy and reproducibility across diverse host and gut microbes. Biomarker-guided and tissue-restricted regulation of the gut microbes–metabolites–Wnt axis may therefore offer a more precise strategy for treating lipid-metabolism-related diseases.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the authors used ChatGPT in order to assist with figure layout and design. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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AUTHOR CONTRIBUTIONS

Cuimei He performed literature collection, figure design, initial drafting, and manuscript revision. Chunxin Liu contributed to the initial drafting of the manuscript. Jie Ma conceived the study and designed the overall framework and provided critical scientific input and conceptual guidance. Jie Yin, Yixing Li, and Yulong Yin contributed to manuscript revision. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests. Yulong Yin is an Editorial Board member of The Innovation Nutrition and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.

DATA AND CODE AVAILABILITY

No new data or code were generated in this study.