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REVIEW

Regulatory effect of Wnt signaling on mitochondria in cancer: from mechanism to therapy

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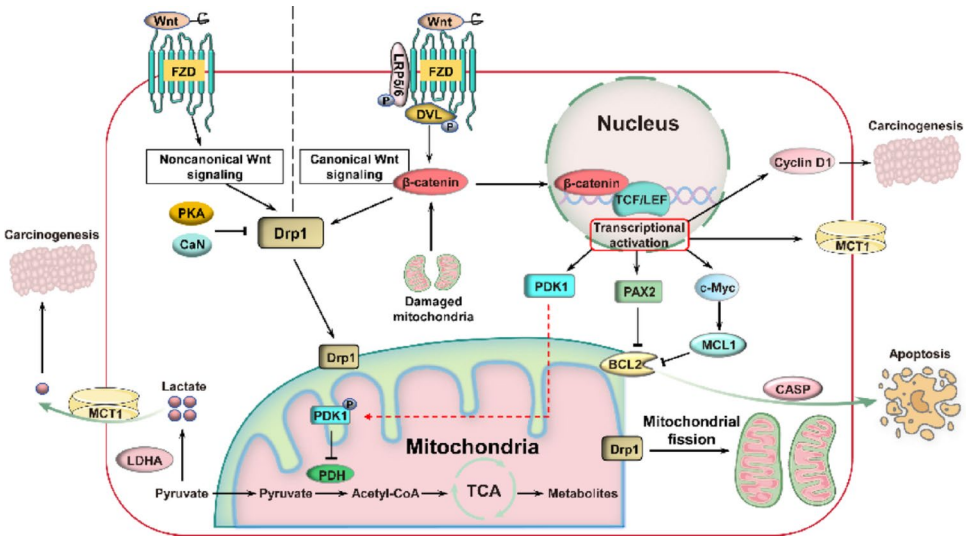
Abstract

Cancer is one of the most significant public health challenges in the new millennium, and complex mechanisms are at work to contribute to its pathogenesis and progression. The Wnt signaling pathways, which are crucial conserved cascades involved in embryological development and tissue homeostasis, and mitochondria, the intracellular powerhouses responsible for energy production, calcium and iron homeostasis, as well as mitochondrial apoptosis in eukaryotic cells, have their own mechanisms regulating these pathological processes. In the past decade, accumulating evidence has indicated that Wnt signaling pathways directly regulate mitochondrial biogenesis and function under physiological and pathological conditions. In this review, we systemically summarize the current understanding of how Wnt signaling pathways, particularly the canonical Wnt cascade, regulate mitochondrial fission, respiration, metabolism, and mitochondrial-dependent apoptosis in cancer. In addition, we discuss recent advancements in the research of anticancer agents and related pharmacological mechanisms targeting the signaling transduction of canonical Wnt pathway and/or mitochondrial function. We believe that the combined use of pharmaceuticals targeting Wnt signaling and/or mitochondria with conventional therapies, immunotherapy and targeted therapy based on accurate molecular pathological diagnosis will undoubtedly be the future mainstream direction of personalized cancer treatment, which could benefit more cancer patients.

Graphical abstract



Keywords Wnt signaling pathways · Cancer · Mitochondrial fission · Mitochondrial biogenesis · Apoptosis · Targeted therapy

Extended author information available on the last page of the article

Abbreviations

AML	Acute myeloid leukemia
APC	Adenomatous polyposis coli
ATC	Anaplastic thyroid cancer
ATP	Adenosine triphosphate
BCL2	B-cell lymphoma 2
BCL9	B-cell CLL/lymphoma 9
BRG1	Brahma-related gene 1
CaMKII	Calmodulin-dependent protein kinase II
CaN	Calcineurin
CASP9	Caspase 9
CCCP	Carbonyl cyanide m-chlorophenylhydrazone
CHD6	Chromodomain helicase DNA-binding protein 6
CK1α	Casein kinase 1α
CRC	Colorectal cancer
CSCs	Cancer stem cells
CYC	Cytochrome C
DKKs	Dickkopf Wnt signaling pathway inhibitors
DPSCs	Dental pulp stem cells
Drp1	Dynamin-related protein 1
DVLs	Dishevelled segment polarity proteins
ER	Endoplasmic reticulum
Fis1	Fission protein 1
FZDs	Frizzled receptors
GC	Gastric cancer
GLS	Glutaminase
Glut	Glucose transporter
GSK- 3β	Glycogen synthase kinase-3β
HCC	Hepatocellular carcinoma
HIF1α	Hypoxia inducible factor 1 subunit α
LATS2	Large tumor suppressor kinase 2
LDHA	Lactate dehydrogenase A
LRP5/6	Low-density-lipoprotein receptor related protein 5/6
MCL1	Myeloid cell leukemia 1
MCT1	Monocarboxylate transporter 1
Mff	Mitochondrial fission factor
NFAT	Nuclear factor of activated T cells
NLK	Nemo-like kinase
NRF1	Nuclear respiratory factor 1
OXPHOS	Oxidative phosphorylation
PAB	Pseudolaric acid B
PANX1	Pannexin 1
PAX2	Paired box 2
PCP	Planar cell polarity
PDH	Pyruvate dehydrogenase
PDK1	Pyruvate dehydrogenase kinase 1
PGAM5	Mitochondrial serine/threonine phosphatase phosphoglycerate mutase family member 5
PGC1α	Peroxisome proliferator-activated receptor gamma coactivator 1α
PI3 K	Phosphoinositide 3-kinase
PKA	Camp-dependent protein kinase
PKC	Protein kinase C
PKM2	Pyruvate kinase M2
PLC	Phospholipase C
PMPCB	Mitochondrial-processing peptidase subunit beta
PORCN	Porcupine
RAC1	Rac family small gtpase 1
ROCK	Rho-associated coiled-coil containing protein kinase
RORα	Retinoic acid-related orphan nuclear receptor α
ROR1/2	Receptor tyrosine kinase-like orphan receptor 1/2
ROS	Reactive oxygen species
RYK	Receptor like tyrosine kinase
SFRPs	Secreted frizzled-related proteins
SLCs	Stem-like cells
TCA	Tricarboxylic acid
TCF/LEF	T-cell factor/lymphoid enhancer factor
TFAM	Mitochondrial transcription factor A
TLE	Transducin-like enhancer protein
TNBC	Triple-negative breast cancer
TNK	Tankyrase

Introduction

Cancer significantly impacts human health, with its incidence and mortality rates rapidly increasing globally, making it the second leading cause of death worldwide. According to most recent data from the International Agency for Research on Cancer, only in 2022, an estimated 20 million new cancer cases were reported globally, with an incidence rate of 196.9 per 100,000. Of these, lung cancer had the highest prevalence, with nearly 2.5 million new cases, accounting for 12.4% of all cancer types worldwide, followed by female breast cancer (11.6%), colorectal cancer (9.6%), prostate cancer (7.3%), and stomach cancer (4.9%) [1]. Currently, the primary strategies for cancer treatment include surgery, chemotherapy, and radiotherapy [2]. Among these, surgery is particularly effective for solid tumors, whereas there is a risk that cancer cells may remain at the surgical margins or circulate postoperatively, increasing the chances of distant metastasis and local recurrence [3]. Furthermore, cytotoxic drugs used in chemotherapy not only target cancer cells but also damage normal cells, resulting in suboptimal therapeutic outcomes. Chemotherapeutic agents such as paclitaxel and doxorubicin also carry the risk of accelerating metastasis. In recent decade, the advent of innovative therapies, such as targeted therapy and immunotherapy, has brought

new hope to cancer patients [4, 5]. Compared to traditional treatment methods, these therapies offer higher precision and lower toxicity, greatly improving patient survival rates. However, they also present drawbacks, such as secondary resistance and low efficacy when used alone [6]. The complexity and heterogeneity of cancer necessitate personalized treatment plans for each patient. Therefore, only by thoroughly elucidating the mechanisms of cancer occurrence and malignant progression can we develop personalized medical strategies for patients, fundamentally improving their overall survival rates and quality of life.

The pathogenesis of cancer involves abnormalities in multiple factors and their interaction, including gene mutations, the tumor microenvironment, intercellular signal transduction, and metabolic reprogramming. Metabolic reprogramming is a hallmark of cancer, enabling cancer cells to survive, proliferate, migrate, and invade under harsh conditions of limited nutrients, hypoxia, and immune surveillance [7]. Mitochondria play a crucial role in the metabolic reprogramming of cancer cells. To meet the metabolic demands of cancer cells, mitochondria can modulate their metabolism by exchanging or modifying subunits of the respiratory chain, switching from oxidative phosphorylation to aerobic glycolysis, lowering the levels of tricarboxylic acid (TCA) cycle intermediates, adapting to reactive oxygen species (ROS) production, decreasing mitochondrial quality, and reducing β-oxidation. This adaptation allows cancer cells to fulfill their metabolic needs in hypoxic environments [8–10]. Notably, extensive studies indicates that Wnt signaling pathways, which are conserved cascades for embryonic development and tissue maintenance, also play a key regulatory role in this process. Dysregulation of Wnt signaling pathways, especially the overactivation of canonical Wnt signaling, can promote mitochondrial biogenesis and energy production, thereby enhancing the energy supply for cancer cells and promoting their proliferation. Interestingly, aerobic glycolysis not only promotes cancer growth but also plays a significant role in human fetal development. Lactate production via aerobic glycolysis is a characteristic feature of the human placenta. During the early stages of human embryonic stem cell differentiation, acetyl-CoA produced through glycolysis loses its function rapidly, leading to a loss of pluripotency. Inhibiting acetyl-CoA consumption is helpful for the maintenance of pluripotency but delays differentiation [11]. Park et al. found that in human dental pulp stem cells (DPSCs), short-term exposure of DPSCs to the activators of canonical Wnt signaling upregulates glycolysis without inducing the aerobic glycolysis. Most glucose is directly converted to pyruvate and mitochondrial acetyl-CoA, resulting in increased reducing power and mitochondrial hyperpolarization. Meanwhile, genes involved in cytosolic acetyl-CoA biosynthesis, such as ATP-citrate lyase, were significantly upregulated in DPSCs after activation of canonical Wnt signaling. This facilitates the conversion of mitochondrial citrate to cytoplasmic acetyl-CoA, thereby providing the main substrate for lipid biosynthesis and maintaining the pluripotency of DPSCs [12].

In this review, we systematically summarize how abnormalities in Wnt signaling pathways, particularly the canonical Wnt signaling, contribute to the pathogenesis and progression of cancer by regulating mitochondrial biogenesis and functions. Additionally, we review recent advancements in anticancer drugs targeting canonical Wnt signaling and/or mitochondria, explores their mechanisms of action, and evaluates their potential applications and clinical trials, aiming to provide new strategies for personalized cancer treatment.

Mitochondria and Wnt signaling pathways

Mitochondria

Mitochondria, double-membraned organelles found in most eukaryotic cells, typically have diameters ranging from 0.5 to 1.0 microns. The prevailing hypothesis suggests that early eukaryotic cells engulfed Gram-negative aerobic bacteria under specific conditions. Over time, these bacteria evolved to live symbiotically with their eukaryotic hosts, eventually becoming mitochondria [13]. Mitochondria generate adenosine triphosphate (ATP) via the respiratory chain and function as the energy centers of the cell. Additionally, they are crucial for regulating various catabolic and anabolic processes, maintaining calcium and iron ion homeostasis, and participating in various signaling pathways, earning them the moniker “powerhouse of the cell” [14, 15]. In the context of cancer, mitochondria are crucial not only for the metabolic needs, proliferation, and metastasis of cancer cells but also for controlling the production and release of ROS, oncoproteins, and tumor metabolites. They regulate calcium ion homeostasis and autophagy processes and influence cancer cell metabolism through intricate mechanisms, thereby enhancing the plasticity of cancer cells and contributing to their malignant growth and metastasis [16, 17]. Thus, mitochondria are central to cellular metabolic and signaling networks, crucially affecting cell fate and maintaining cellular homeostasis. Understanding the regulatory mechanisms and functions of mitochondria in cancer cell metabolism and targeting them could open new avenues for cancer treatment.

Wnt signaling pathways

The Wnt signaling pathways are evolutionarily conserved cascades triggered by various Wnt ligands, which are

cysteine-rich secreted glycoproteins with 19 members in humans [18, 19]. Physiological Wnt signaling pathways play a crucial role in the growth, development and maintenance of homeostasis of living organisms through regulation of the basic processes in living cells, such as cell differentiation, proliferation, and apoptosis [20–22]. Disruption in Wnt signaling, undoubtedly, can lead to the pathogenesis of various human diseases, particularly cancers [23–28]. Wnt signaling is divided into the β-catenin-dependent (canonical) and β-catenin-independent (noncanonical) pathways. The canonical pathway is well-studied, with nuclear β-catenin accumulation indicating activation **(**Fig. 1**)** [29]. Specifically, in the absence of Wnt ligands, β-catenin is phosphorylated by the two kinases glycogen synthase kinase- 3β (GSK- 3β) and casein kinase 1α (CK1α) in the destruction complex, followed by ubiquitinated by SCFβTrCP and subsequently degraded by proteasome. In contrast, when Wnt ligands are sufficient, they bind to corresponding frizzled receptors (FZDs) and the coreceptor low-density-lipoprotein receptor related protein 5/6 (LRP5/6) on the cell membrane, triggering LRP6 phosphorylation and the sequential recruitment of Dishevelled segment polarity proteins (DVLs), Axin, and GSK- 3β. This disrupts the stabilization of the destruction complex, allowing β-catenin to accumulate in the cytoplasm, translocate to the nucleus, and activate T-cell factor/lymphoid enhancer factor (TCF/LEF)-mediated transcription of target genes. This activation occurs through the displacement of transcriptional corepressors such as Groucho/transducin-like enhancer protein (TLE) on TCF/LEF and the recruitment of transcriptional coactivators including B-cell CLL/lymphoma 9 (BCL9), Brahma-related gene 1 (BRG1), CBP/p300, and Pygo. Importantly, most downstream target genes of this cascade, such as Axin2, c-Myc and cyclin D1, are crucial regulators of cell fate. Aberrant activation of this canonical signaling, due to the downregulation or inactivating mutations of negative regulators such as adenomatous polyposis coli (APC), or the upregulation or activating mutations of positive regulators such as β-catenin, can therefore contribute to the malignant transformation of normal cells, cancer development, and metastasis [30].

The noncanonical pathways primarily include the Wnt/Ca^{2+} and Wnt/planar cell polarity (PCP) signaling pathways. Ligands such as Wnt5a, Wnt5b, and Wnt11 specifically bind to FZDs and G proteins, inducing phospholipase C (PLC) activation and Ca^{2+}-dependent pathways. This leads to the activation of transcription factors such as nuclear factor of activated T cells (NFAT) and Nemo-like kinase (NLK), as well as the phosphorylation of retinoic acid-related orphan nuclear receptor α (RORα), ultimately regulating cell migration and adhesion. Additionally, ligands such as Wnt7a can activate the Wnt/PCP/JNK pathway by binding to certain FZDs and tyrosine kinase coreceptors, including receptor tyrosine kinase-like orphan receptor 1/2 (ROR1/2)

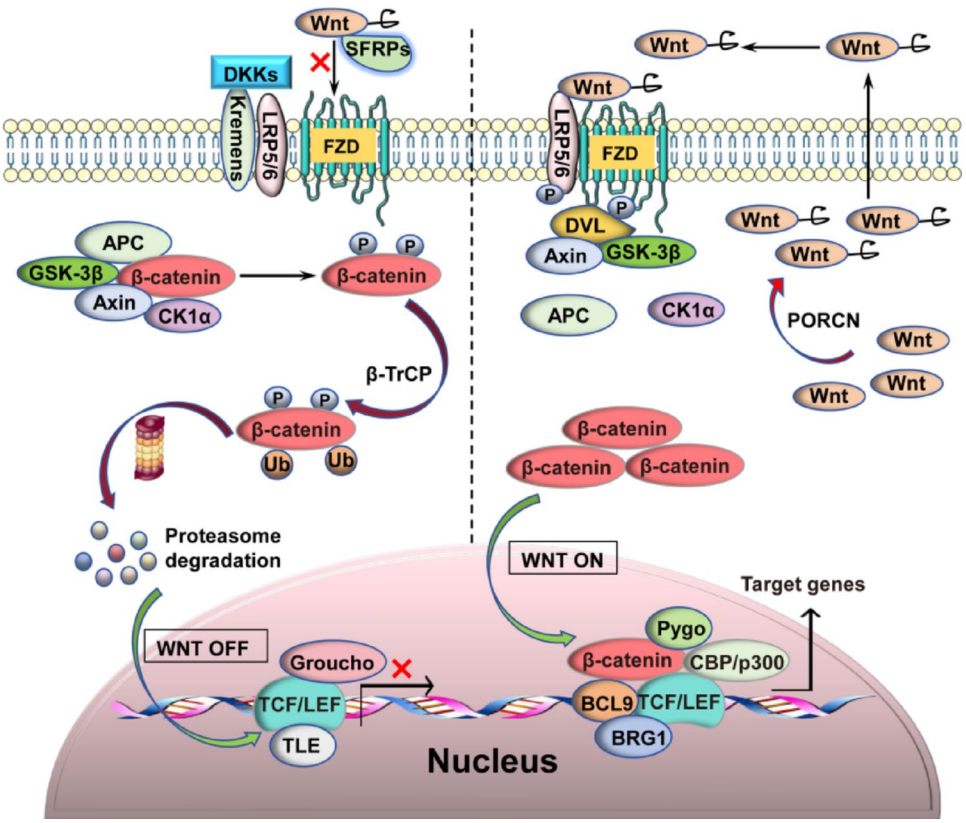


Fig. 1 Schematic summary of signal transduction mechanism of the canonical Wnt signaling in human cells. APC: adenomatous polyposis coli; BCL9: B-cell CLL/lymphoma 9; BRG1: Brahma-related gene 1; CBP: CREB-binding protein; CK1α: casein kinase 1α; DKKs: Dickkopf Wnt signaling pathway inhibitors; DVL: dishevelled segment polarity protein; FZD: frizzled receptor; GSK- 3β: glycogen synthase kinase- 3β; LRP5/6: low-density-lipoprotein receptor related protein 5/6; SFRPs: secreted frizzled-related proteins; TCF/LEF: T-cell factor/lymphoid enhancer-factor; TLE: transducin-like enhancer protein.

and receptor like tyrosine kinase (RYK). This interaction recruits DVLs to activate small Rho GTPases, such as Rac family small GTPase 1 (RAC1) and RhoA, which regulate cell polarization through the activation of JNK pathway mediated by transcription factors such as ATF2 and c-JUN. Furthermore, the activation of RhoA-driven Rho-associated coiled-coil containing protein kinase (ROCK) and JNK plays a crucial role in cytoskeletal organization. Noncanonical Wnt/PCP signaling controls asymmetric cytoskeletal modulation and cellular polarization [13]. The specific mechanisms by which particular Wnt ligands activate distinct Wnt signaling pathways remain largely unknown. It is hypothesized that the spatial distribution and expression pattern of specific Wnt ligands, downstream Wnt receptors, and components may dictate distinct Wnt signaling responses. Unlike canonical Wnt signaling, which predominantly initiates and drives the malignant progression of most cancers, noncanonical Wnt pathways exhibit a dual role, either inhibiting or promoting cancer development [31, 32]. The predominant effect may depend on the specific cancer type and the tumor microenvironment. In specific contexts, these pathways can even suppress cancer progression by inhibiting canonical Wnt signaling [33].

Regulatory effect of Wnt signaling on mitochondria in physiological conditions

Mitochondria are essential hubs for intercellular signal transduction and are modulated by various signaling pathways. Extensive research has demonstrated that the Wnt signaling pathways play a crucial role in regulating mitochondrial biogenesis, dynamics, and metabolism. Mitochondrial biogenesis is a regenerative process that maintains mitochondrial quantity by replacing worn-out and damaged mitochondria with new, healthy ones. Evidence suggests that treating cells with Wnt ligands or inhibiting negative regulators of the Wnt signaling pathways can enhance mitochondrial numbers. Additionally, an in vitro study found that mitochondrial serine/threonine phosphatase phosphoglycerate mutase family member 5 (PGAM5), released from damaged mitochondria, interacts with the scaffold protein Axin1 from the destruction complex, facilitating β-catenin dephosphorylation and subsequently activating canonical Wnt signaling to induce mitochondrial biogenesis. Stable expression of PGAM5 can increase the formation of new mitochondria by 30–40% [34].

Mitochondrial dynamics refer to the balance between mitochondrial fusion and fission, optimizing ATP production efficiency. These dynamics are therefore intimately connected to mitochondrial functions such as cell proliferation, migration, and metabolism, and are regulated by various enzymes and proteins. Both canonical and noncanonical Wnt signaling pathways have been shown to regulate intracellular mitochondrial distribution and dynamics. Inhibition of these pathways can lead to mitochondrial dysfunction, contributing to neurodegenerative diseases such as Alzheimer's disease [35]. Chromodomain helicase DNA-binding protein 6 (CHD6) has been shown to enhance the transcription of TMEM65, a mitochondrial inner membrane protein involved in ATP production and mitochondrial dynamics, by activating the canonical Wnt signaling, thereby promoting colorectal cancer (CRC) development [36]. In the noncanonical Wnt/Ca^{2+} pathway, the Wnt5a ligand binds to its receptor FZD, increasing intracellular calcium ion concentrations from the endoplasmic reticulum and activating proteins such as protein kinase C (PKC), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), and calcineurin (CaN). These proteins, in turn, activate dynamin-related protein 1 (Drp1, encoded by DNM1L) by translocating it from the cytoplasm to the outer mitochondrial membrane, leading to mitochondrial fission [37].

The oxidative phosphorylation of the mitochondrial respiratory chain supplies the energy required for various cellular activities and is closely connected to mitochondrial biogenesis, dynamic changes, and ROS generation. Studies have found that decreased activity of Wnt ligands is associated with secreted frizzled-related proteins (SFRPs), among which SFRP5 is believed to increase in adipocytes during obesity, possibly to counteract Wnt signaling pathway transduction. Treating EMSC adipocytes with Wnt3a for 48 h increased the basal oxygen consumption rate of the cells. Consequently, the absence of SFRP5 in adipose tissue enhances Wnt signal transduction, stimulating mitochondrial biogenesis and oxidative phosphorylation, leading to resistance to adipocyte growth under obesogenic conditions in mice [38]. Continuous incubation of cells with Wnt3a for two weeks also significantly increased mitochondrial ROS synthesis.

Regulatory effect of Wnt signaling on mitochondria in cancer

Regulating role of Wnt signaling in mitochondrial fission in cancer

Mitochondrial fission is recognized as an effective mechanism for promoting apoptosis by inhibiting anti-apoptotic factors. This process is regulated by Drp1, which primarily resides in the cytoplasm but is recruited to the mitochondrial surface, where it forms ring-like oligomers that encircle and utilizes GTP hydrolysis to power the constriction and division of the outer mitochondrial membrane **(**Fig. 2**)**. Several

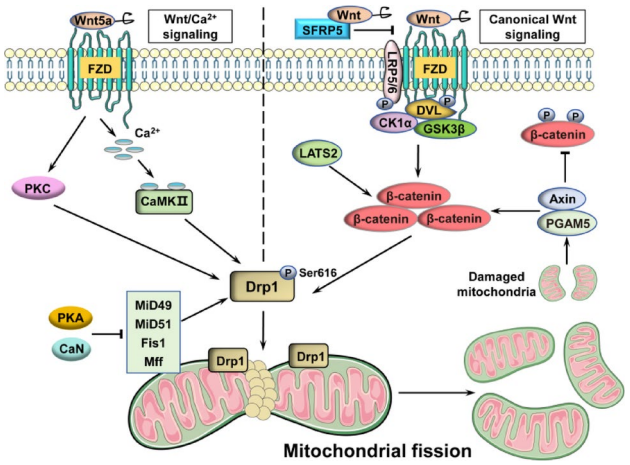


Fig. 2 Schematic summary of the regulating role of Wnt signaling in mitochondrial fission in cancer. CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; CaN: calcineurin; CK1α: casein kinase 1α; Drp1: dynamin-related protein 1; DVL: dishevelled segment polarity protein; Fis1: fission protein 1; FZD: frizzled receptor; GSK- 3β: glycogen synthase kinase- 3β; LATS2: large tumor suppressor kinase 2; LRP5/6: low-density-lipoprotein receptor related protein 5/6; Mff: mitochondrial fission factor; PGAM5: phosphoglycerate mutase family member 5; PKC: protein kinase C; SFRP5: secreted frizzled-related proteins 5

receptor proteins on the outer mitochondrial membrane, including fission protein 1 (Fis1), mitochondrial fission factor (Mff), MiD49, and MiD51, are essential for the recruitment of Drp1 to the mitochondria [39]. Most mitochondrial fission relies on the Drp1 protein. Drp1 can be activated in various ways to drive mitochondrial fission in mammalian cells, including interaction with mitochondrial Drp1 receptors, post-translational modifications of Drp1, interaction with the actin cytoskeleton or mitochondrial lipid cardiolipin, and contact with various organelles, such as the endoplasmic reticulum (ER), lysosomes, and Golgi-derived vesicles. Additionally, Drp1 can be phosphorylated at serine 616 (Ser616) by ERK or cyclin-dependent kinases, which enhances its capacity to induce mitochondrial fission. Conversely, cAMP-dependent protein kinase (PKA) and CaN inhibit mitochondrial fission by disrupting the interaction between Drp1 and MiD49/51 and the subsequent dephosphorylation of Drp1 at Ser637 [40, 41]. As a classical ligand for noncanonical Wnt signaling, Wnt5a has been identified as an inducer of $Drp1^{Ser616}$ phosphorylation in neurons, promoting mitochondrial fission. Interestingly, a recent study has demonstrated that the uptake of fatty acids can induce mitochondrial fission in CRC cells, providing metabolic plasticity for tumorigenesis by promoting ERK-dependent $Drp1^{Ser616}$ phosphorylation. This phosphorylation enhances Drp1 dimerization and interaction with Mff, and also activates canonical Wnt signaling by increasing acetyl-CoA production and subsequent β-catenin acetylation [42]. Consequently, knockdown of Drp1 significantly reduces the formation of tumor organoids in vitro and xenograft tumor growth in vivo by preventing fatty acid oxidation-dependent canonical Wnt signaling [43]. Large tumor suppressor kinase 2 (LATS2) also plays a significant role in the apoptotic response pathway and is associated with the progression of various cancers. Chen and colleagues have shown that in hepatocellular carcinoma (HCC), LATS2 upregulates Drp1 expression via activation of the canonical Wnt signaling. Inhibition of this cascade could abolish LATS2-induced Drp1 upregulation and mitochondrial fission, as well as mitochondrial dysfunction, ultimately sustaining the viability of cancer cells [44]. Additionally, Katajisto and colleagues discovered an uneven distribution of mitochondria during the asymmetric division of stem-like cells (SLCs). Using a mammary SLCs model, they observed that newly synthesized mitochondria concentrate in the stem cells, while older mitochondria are allocated to the daughter cells. This process is Drp1-dependent and is crucial for the maintenance of stemness and the SLC pool [45, 46].

Regulating role of Wnt signaling in mitochondrial respiration in cancer

During cancer development, the Wnt signaling pathways not only facilitate cancer cells in evading apoptosis by regulating mitochondrial fission but also drive their proliferation by promoting Warburg metabolism and regulating the cell cycle [47–49]. The malignant proliferation of cancer cells necessitates a large amount of energy supply. To sustain their rapid growth, cancer cells adopt an alternative energy acquisition pathway known as aerobic glycolysis, or the Warburg effect [50, 51]. This effect requires changes in two key enzymes involved in glucose metabolism, one of which is pyruvate dehydrogenase kinase 1 (PDK1) [52]. Canonical Wnt signaling activates the phosphoinositide 3-kinase (PI3 K)/Akt pathway, which activates hypoxia inducible factor 1 subunit α (HIF1α) and subsequently stimulates aerobic glycolysis-related enzymes, including glucose transporter (Glut), PDK1, lactate dehydrogenase A (LDHA), and monocarboxylate transporter 1 (MCT1). Phosphorylation of PDK1 inhibits the pyruvate dehydrogenase (PDH) complex, preventing most pyruvate from converting into acetyl-CoA in the mitochondria and limiting the amount of acetyl-CoA entering the TCA cycle **(**Fig. 3**)**. Despite the presence of oxygen, cancer cells primarily rely on aerobic glycolysis for energy production [52]. Consequently, pyruvate in the cytoplasm is converted into lactate through the activation of LDHA, and MCT1 facilitates lactate extrusion from the cytoplasm. The increased lactate in the internal environment promotes vascular endothelial growth factor expression, contributing to the formation of the tumor microenvironment and accelerating cancer progression [47, 52].

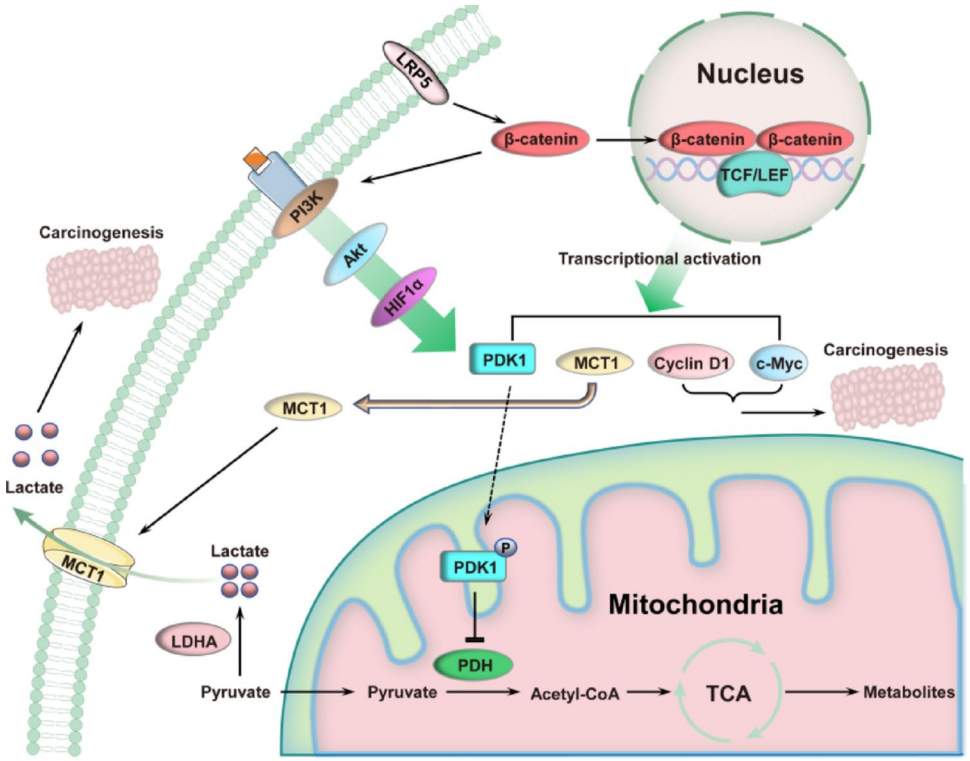


Fig. 3 Schematic summary of the regulating role of Wnt signaling in mitochondria respiration in cancer. HIF1α: hypoxia inducible factor 1 subunit α; LDHA: lactate dehydrogenase A; LRP5: low-density-lipoprotein receptor related protein 5; MCT1: monocarboxylate transporter 1; PDH: pyruvate dehydrogenase; PDK1: pyruvate dehydrogenase kinase 1; PI3 K: phosphoinositide 3-kinase; TCA cycle: tricarboxylic acid cycle; TCF/LEF: T-cell factor/lymphoid enhancer-factor

Therefore, blocking any step in aerobic glycolysis can theoretically reduce the energy supply of cancer cells and inhibit their malignant progression. Vitamin C inhibits β-catenin/TCF/LEF-induced c-Myc overexpression by preventing the phosphorylation of pyruvate kinase PKM2, downregulating Glut1 and pyruvate kinase M2 (PKM2) expression, which results in a major inhibition of the Warburg effect and energetic stress in KRAS mutant colon cancer [53]. Our previous study demonstrates that overexpressing LRP5, an indispensable coreceptor for canonical Wnt signaling, enhances the malignant phenotypes of gastric cancer (GC) cells and reduces their sensitivity to chemotherapeutic drug such as cisplatin. Mechanistically, upregulated LRP5 in GC cells activates canonical Wnt signaling and further induces aerobic glycolysis by simultaneously decreasing mitochondrial content and stimulating the expression of enzymes and regulator involved in this metabolic pathway, including GLUT1, HK2, LDHA, PKM2, and HIF1α, thereby increasing their energy supply [54]. Treating cancer cells with dichloroacetate, a PDK inhibitor, dominant-negative LEF1, or Wnt inhibitor XAV939 can inhibit aerobic glycolysis but increase oxidative phosphorylation (OXPHOS) by targeting PDK1 or MCT1 [55, 56]. Notably, PDK1 and MCT1 have been proven to be the direct target genes of canonical Wnt signaling for Warburg metabolism in several types of cancer, such as CRC [56]. Conversely, high glucose levels can increase the nuclear translocation of β-catenin following Wnt activation. Mutations in the N-terminus of β-catenin are present in 10% of sporadic colorectal cancers and 20% of HCC [57]. These mutations stabilize β-catenin, enabling it to evade the destruction complex and activate the canonical Wnt signaling, thereby promoting tumorigenesis. However, these active mutations decrease the rate of aerobic glycolysis in cancer cells, rendering them reliant on mitochondrial oxidative phosphorylation for survival. Therefore, treating cancer cells harboring mutant β-catenin with mitochondrial uncouplers such as nonactin, valinomycin, and carbonyl cyanide m-chlorophenylhydrazone (CCCP) could selectively induce apoptosis by inhibiting mitochondrial OXPHOS without affecting normal cells [57]. Interestingly, mitochondrial respiration, in turn, regulates the activation of canonical Wnt signaling. Knockdown of mitochondrial transcription factor A (TFAM), an essential regulator of mitochondrial DNA replication and transcription, directly inhibits the transcriptional activation of canonical Wnt signaling in CRC cells. This inhibition subsequently suppresses the expression of several downstream target genes associated with cancer stem cells (CSCs) stemness, such as CD44, MYC, and CD133. Notably, intestinal-specific deletion of TFAM prevents tumorigenesis in APC-driven CRC mouse models by decreasing canonical Wnt signaling, suggesting that inhibiting mitochondrial content or respiration presents an effective strategy for combating canonical Wnt signaling-driven cancers [58].

Regulating role of Wnt signaling in mitochondrial metabolism in cancer

Aerobic glycolysis is a prevalent metabolic reprogramming observed in cancer cells; however, this does not necessarily indicate mitochondrial dysfunction. Research has demonstrated that mitochondria in most cancer cells can function as signaling organelles, regulating cell proliferation and carcinogenesis through the release of certain metabolites and proteins [59]. ROS, primarily produced by mitochondrial OXPHOS, are normal byproducts of cellular respiration and can exert opposite effects depending on their concentration. In normal cells, low ROS concentrations can fulfill physiological functions. In contrast, cancer cells exhibit reduced ROS clearance, leading to an excessive increase in ROS levels. Disturbance in ROS generation and clearance pathways is a common feature of cancer cells [60, 61]. A recent study reported that IR- 251, a mitochondrion-targeting near-infrared fluorophore probe, exhibits excellent anti-cancer proliferation and metastasis abilities. Its mechanism of action is primarily through the induction of ROS generation by inhibiting peroxisome proliferator activated receptor γ, subsequently inhibiting the canonical Wnt signaling and the expression of downstream target genes related to the cell cycle and metastasis [62]. Similarly, chloroquine was found to inhibit autophagy and paclitaxel resistance of lung cancer cells, attenuate their metastatic potential by increasing the accumulation of damaged, superoxide-producing mitochondria, and ROS overproduction, leading to a decline in ROS-mediated Akt activity and canonical Wnt signaling. Therefore, restoring the disturbed ROS concentration is a viable strategy for cancer treatment [63].

As a pivotal factor in the canonical Wnt signaling, β-catenin also serves as a regulatory hub in multiple cellular processes such as metabolism and energy homeostasis. To elucidate the specific functions of β-catenin, Daniele et al.. knocked out the *CTNNB1* gene, which encodes β-catenin in the breast cancer cells and found that downregulation of β-catenin inhibited the expression of several transcription factors regulating mitochondrial biogenesis, including peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α), TFAM, and nuclear respiratory factor 1 (NRF1), decreased carbohydrate metabolism and TCA cycle related protein levels, increased proteins involved in lipid metabolism, exogenous fatty acid uptake and triglyceride mobilization [64]. Pannexin 1 (PANX1), a member of the pannexin family of channel-forming glycoproteins, plays important roles in physiological processes such as wound healing and pathological disorders such as cancer. Penuela and colleagues have shown that there is direct interaction between PANX1 and β-catenin. Inhibition of the PANX1 could downregulate β-catenin expression, decrease mitochondrial respiration activity, impair metabolic function of melanoma cells, and serve as a potential target for treating melanoma [65, 66]. To test whether mitochondrial metabolic stress could in turn modulate canonical Wnt signaling, Costa et al.. treated CRC cells and zebrafish with sublethal concentrations of different compounds with known effects on respiratory chain complexes, and found that a decrease in mitochondrial ATP production could specifically downregulate canonical Wnt signaling via inducing ER stress both in vitro and in vivo, revealing a mitochondrial-Wnt signaling axis [67]. However, the exact mechanism requires further investigation. Together, aerobic glycolysis is an adaptation of cancer cells to their environment, primarily achieved through mitochondrial alterations. This also means mitochondria in cancer cells are more susceptible to disturbances than those in normal cells. Therefore, disrupting mitochondria in cancer cells by targeting Wnt signaling-mediated aerobic glycolysis is a promising therapeutic strategy.

Regulating role of Wnt signaling in mitochondrial-dependent apoptosis in cancer

It is well established that a key mechanism by which the Wnt pathways promote cancer proliferation is through the regulation of the cell cycle. The cell cycle encompassed the entire series of processes from the completion of one division to the conclusion of the next and acts as a critical regulator of cell proliferation [68]. Apoptosis, a programmed cell death, is the natural endpoint and an essential process in the cellular life span, typically occurring when the cell cycle halts [69]. Two main pathways trigger cellular apoptosis: the cell death receptor pathway and the mitochondria-initiated pathway. Inhibiting the malignant proliferation of cancer cells and inducing their apoptosis are crucial mechanisms of action for most current anti-cancer strategies. Mitochondrial damage can induce apoptosis, with the loss of mitochondrial membrane potential serving as a critical indicator. The B-cell lymphoma 2 (BCL2) family proteins are key regulators of apoptosis, controlling mitochondrial membrane potential and modifying mitochondrial outer membrane permeability. The two most pivotal members of this protein family are the antiapoptotic protein BCL2 and the proapoptotic protein Bax. Disruption of mitochondrial membrane potential can give rise to the release of cytochrome C (CYC) and the activation of caspase family proteases in the mitochondrial-dependent apoptosis pathway. The caspase family responds to proapoptotic signals, among which caspase 9 acts as an initiator. Cleavage of caspase 9 (CASP9) can activate downstream effector caspases, such as CASP3 or CASP7, promoting DNA damage-induced apoptosis in a PARP-dependent manner [70]. Studies have

shown that the degradation of β-catenin induced by inhibition of the canonical Wnt signaling is capable of promoting cell cycle arrest and caspase-dependent apoptosis in several types of cancer **(**Fig. 4**)** [3, 71–73].

Paired box 2 (PAX2), a member of the PAX transcription factor family, is highly expressed in kidney and gonad-related tumors and is considered a biomarker for the development of reproductive-related cancers. In cervical cancer cells, canonical Wnt signaling is abnormally activated, and the promoter of the proapoptotic gene *BAX* contains PAX2 binding sites. Activation of this canonical cascade can increase PAX2 expression, thereby inhibiting Bax expression and cellular apoptosis. Fortunately, the activation of this PAX2/Wnt/antiapoptotic axis can be effectively abolished by treating with Pseudolaric acid B (PAB), a natural biologically active diterpenoid extracted from the bark of *Pseudolarix kaempferi* [74]. As an antiapoptotic member of the BCL2 protein family, myeloid cell leukemia 1 (MCL1) contributes to carcinogenesis and treatment resistance, making it a focal point in the search for anti-cancer drugs [75]. Interestingly, *c-Myc*, a classical Wnt-responsive gene, directly controls MCL1 transcription. It has been reported that the Wnt5b/MCL1 cascade is crucial for the survival of triple-negative breast cancer (TNBC). Wnt5b is upregulated in TNBC and TNBC-derived cell lines and is significantly associated with c-Myc. It controls mitochondrial biogenesis and maintains mitochondrial quality and function by upregulating MCL1 through the activation of canonical Wnt signaling. Downregulation of Wnt5b can therefore bring about cell cycle arrest and caspase-independent death due to reduced mitochondrial quality, as evidenced by compromised mitochondrial DNA (mtDNA) and OXPHOS [76]. Therefore, pharmacologically inhibiting the canonical Wnt pathway to induce mitochondrial-dependent apoptosis is a promising approach for cancer treatment.

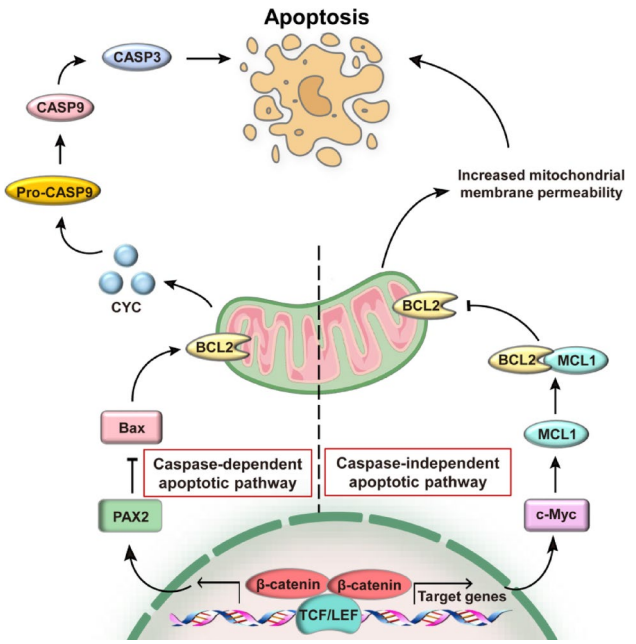


Fig. 4 Schematic summary of the regulating role of Wnt signaling in mitochondrial-dependent apoptosis in cancer. BCL2: B-cell lymphoma 2; CASP3: caspase 3; CASP9: caspase 9; CYC: cytochrome C; MCL1: myeloid cell leukemia 1; PAX2: paired box 2; TCF/LEF: T-cell factor/lymphoid enhancer-factor.

The application of anticancer treatment targeting Wnt signaling and/or mitochondria

Preclinical studies and clinical trials on agents targeting Wnt signaling in cancers

With the advancement in understanding Wnt signaling pathways, various targeted agents have been developed, many of which have shown promising clinical potential in cancer treatment. Due to a clearer understanding of the signal transduction mechanism of the canonical Wnt signaling, current therapeutic research is focused primarily on this cascade. The related agents are categorized into four main types based on the specific step they target in the sequence of canonical Wnt signal transduction [77]. Given that numerous comprehensive review articles have systemically summarized the mechanisms of action and therapeutic efficacy of current canonical Wnt signaling-based agents in the treatment of various cancer types during laboratory and clinical stages [78, 79], we will provide only a concise overview of their mechanisms of action and discuss the associated advantages and disadvantages.

The first category of canonical Wnt signaling-based agents primarily suppress the normal activity and secretion of all Wnt ligands. Among them, porcupine inhibitors are the most representative, as they deactivate the activity and secretion of all Wnt ligands by inhibiting the membrane-bound O-acyltransferase porcupine (PORCN)-mediated palmitoylation at specific serine residues. Inhibitors of Wnt production (IWPs) are the first class of PORCN inhibitors with varying half maximal inhibitory concentrations (IC50), including IWP- 2, IWP- 3, IWP- 4, IWP- 12, IWP L6, IWP-2-V2, and IWP-O1. Other available PORCN main inhibitors include IWP-L6, Wnt-C59, LGK974, GNF- 6231, and ETC- 159, with Wnt-C59 being the most extensively studied [80, 81]. LGK974 has been evaluated in a phase I, open-label, dose escalation clinical trial (NCT01351103) for treating patients with several advanced cancers dependent on Wnt ligands, demonstrating good tolerance but limited anticancer activity when used as a monotherapy. Further trials are being conducted to evaluate whether the combination of LGK974 with checkpoint inhibitor such as

PDR001 could enhance the efficacy of the latter in treating patients with BRAF mutations [18, 82]. The second category of canonical Wnt signaling-based agents aim to inhibit the reciprocal combination between Wnt ligands and their corresponding receptors and coreceptors. Dickkopf Wnt signaling pathway inhibitors (DKKs) are secreted glycosylated proteins with four members, DKK1 to DKK4, which can function as either antagonists or agonists of canonical Wnt signaling dependent on specific cellular context. Specifically, the interaction of DKKs with cofactor Kremens and LRP6 forms a ternary complex that inhibits the canonical Wnt signaling [83]. In the absence of DKKs, Kremens bind to LRP6, stabilizing its localization on the cell surface and activating the canonical Wnt cascade by inducing LRP6 endocytosis [84]. DKK1 acts as an antagonist of canonical Wnt signaling and as a tumor suppressor in CRC, where it is notably downregulated. Interestingly, DKK1 is also a downstream target of this signaling, capably of initiating a negative feedback loop [85]. Thus, inducting DKK1 expression has an anti-tumoral effect in several types of cancer, including CRC and thyroid cancer [85, 86]. Conversely, DKK1 is overexpressed in pancreatic cancer, while its knockdown can suppress the growth and migratory activates of cancer cells, suggesting a carcinogenic role of DKK1 in this context. Given the pivotal role of the FZD receptors and LRP5/6 coreceptor in canonical Wnt signaling, specific antibodies or antagonists that can decoy them to sequester Wnt ligands, inhibitors that interfere with their activities, or degrading agents that downregulate their expression, theoretically have potential to block canonical Wnt signaling-driven cancers. To take two examples, Salinomycin sodium is a special inhibitor of canonical Wnt signaling, which demonstrates selectively inhibitory activity against various types of cancer and CSCs by blocking Wnt-induced LRP6 phosphorylation and inducing its degradation [87, 88]. Ipafricept (OMP- 54 F28) is a first-in-class recombinant fusion protein with the extracellular domain of human FZD8, allowing it to specifically bind Wnt ligands and inhibit all Wnt signaling. It has demonstrated unique combinational antitumor efficacy with taxanes against chemotherapy-resistant CSCs and various solid tumors by promoting mitotic cell death, all while maintaining good tolerance [89, 90]. Two independent Phase Ib studies investigated Ipafricept in combination with chemotherapeutic agents such as paclitaxel and gemcitabine or with paclitaxel and gemcitabine in patients with advanced pancreatic cancer or recurrent ovarian cancer. These studies demonstrated good tolerance, although one trial was terminated due to potential bone-related toxicity associated with excessive inhibition of normal Wnt-dependent cells and bone homeostasis [91, 92]. The third category of agents targeting canonical Wnt signaling aims to promote the degradation or inhibit the expression of β-catenin. Tankyrase (TNK) inhibitors are the most representative agents in this category. They inhibit canonical Wnt signaling by suppressing the poly-ADP ribosylation of TNK1/2, two enzymes which promote the ubiquitination and proteolysis of Axin, ultimately leading to decreased stabilization of the destruction complex and subsequent inhibition β-catenin degradation [93]. Over 20 specific tankyrase inhibitors with varying oral activities and IC_{50} values have been developed for research on cancer associated with the aberrant activation of the canonical Wnt signaling. These inhibitors have demonstrated significant efficacy in suppressing the growth of most solid tumors. Notably, IWR- 1 and XAV- 939 are the most extensively studied reversible tankyrase inhibitors [94, 95]. In the past decade, engineered proteolysis-targeting chimeras (PROTACs) and CRISPR/Cas9-mediated strategies for sustained β-catenin degradation or knockout have been designed, achieving significant inhibition of canonical Wnt signaling-dependent cancers. These approaches have even shown synergistic effects when combined with immunotherapy, thereby providing new therapeutic avenues for cancer treatment [96–98]. The final category of agents targeting canonical Wnt signaling aims to inhibit the transcriptional activity of the β-catenin/TCF/LEF complex, thereby reducing the expression of downstream oncogenic Wnt target genes. This is achieved by antagonizing the interaction between β-catenin and TCF/LEF, or by inhibiting the recruitment or the activities of transcriptional coactivators involved in this process, such as BCL9, BRG1, CBP/p300, and Pygo2. Notable inhibitors of the β-catenin/TCF/LEF complex, including BC21, chlorquinaldol, LF3, and Toxoflavin, have demonstrated the ability to suppress the malignant phenotypes of various cancer cells. ICG- 001 selectively interferes with the β-catenin/CBP interaction, efficiently inhibiting the progression and metastasis of several types of cancers by binding to CBP rather than p300 [99, 100]. Additionally, CBP/p300 inhibitors such as C646 and curcumin exhibit high selectivity and can inhibit not only β-catenin/TCF/LEF-driven cancers but also androgen receptor signaling-driven androgen-sensitive and castration-resistant prostate cancer [101–103]. Over the past decades, numerous anticancer agents targeting canonical Wnt signaling have been evaluated. However, none has been approved to treat cancer driven by this signaling. Most remain in the investigational phase, with some showing promising anticancer effects and entering clinical trials. Currently, dozens of pharmaceuticals targeting canonical Wnt signaling are in Phase I and Phase II clinical trials for cancer treatment, with very few advancing to Phase III. The main complications associated with these pharmaceuticals include inevitable toxic side effects, particularly gastrointestinal reactions and bone-related diseases, due to the critical role of Wnt signaling in maintaining tissue homeostasis.

Additionally, their poor unavailability remains a significant challenge. For an in-depth understanding of the specific effects and potential complications of Wnt signaling-based pharmaceuticals in clinical cancer therapeutics, please refer to the review article elaborately summarized by Neiheisel and co-workers [104].

Preclinical studies and clinical trials on agents targeting mitochondria in cancers

As aforementioned, mitochondria, which govern the biosynthesis, bioenergetics, and signaling transduction of cells, is crucial for cancer proliferation, survival, and metastasis. Moreover, the distinct metabolic characteristics of mitochondria in cancer cells, as opposed to normal cells, have highlighted mitochondria as a promising target in the research of anticancer drugs. Currently, several agents have been developed to combat and treat cancer by modulating various mitochondrial functions. As a critical carbon source, glutamine maintains the stability of the TCA cycle and its intermediates. Mitochondrial glutaminase (GLS) plays a key role in converting glutamine to glutamate. It has been demonstrated that GLS is overexpressed in several cancer types, including colorectal, prostate, and breast cancers [105]. Inhibiting GLS activity has shown significant antitumor effects in mouse models of lung, kidney, liver cancers, and lymphoma [106]. Consequently, targeting glutamine catabolism to disrupt the energy supply of cancer cells is anticipated to be a potent strategy for cancer therapy. CB- 839, a selective GLS inhibitor, suppresses the crucial metabolic intermediate glutamate, which is vital for macromolecule synthesis, ATP production, and cellular redox balance. This offers therapeutic advantages for patients with TNBC and other glutamine-dependent cancers [107]. The unique energy supply mechanisms of cancer cells are crucial for their initiation, progression, and metastasis. Disruption of the mitochondrial electron transport chain in cancer cells can reduce the efficiency of the TCA cycle, impede ATP production, and interfere with the synthesis of macromolecules essential for cancer growth, ultimately inhibiting tumorigenesis and metastasis. Notably, metformin, an inhibitor of mitochondrial respiratory complex I, has demonstrated anticancer effects in multiple clinical trials. Combining metformin with 2-deoxyglucose can inhibit both mitochondrial respiration and glycolysis in prostate cancer cells, achieving a 96% inhibition rate of cancer cell viability [108]. Other respiratory complex I inhibitors, such as BAY87 - 2243, IACS- 010759, and tamoxifen, have also been shown to induce the death of cancer cells and reduce their proliferation [8]. Vitamin E succinate, another mitochondrial-targeting drug, can simultaneously inhibit respiratory complex I and complex II, thereby suppressing the respiration of breast cancer cells, promoting ROS generation, and inducing apoptosis [109]. Lonidamine, a respiratory complex II inhibitor, also induce melanoma cell death through ROS generation [110]. Given the critical role of mitochondria in cellular communication and signal transduction, targeting mitochondria offers a highly promising strategy for cancer treatment research. Polyphyllin VII, a significant component of Rhizoma Paridis saponins, has demonstrated cytotoxic effects on several types of cancer. Studies has shown that polyphyllin VII can interfere with Drp1 mitochondrial translocation via the PP2 A/Akt pathway, inducing mitochondrial dysfunction characterized by enhanced mitochondrial fission and increased ROS production. This approach is considered effective for treating ovarian cancer [111]. Additionally, The JAK1/2-STAT3 pathway has emerged as a potential therapeutic target for anaplastic thyroid cancer (ATC) due to its significant upregulation in ATC patients. Ge and colleagues have revealed that Ruxolitinib (Ruxo), a JAK1/2 inhibitor, can inhibit STAT3 phosphorylation, suppress Drp1 transactivation, impede mitochondrial fission, and induce apoptosis and gasdermin E pyroptosis through a caspase 9/3-dependent mechanism, thereby achieving therapeutic effects in treating ATC [112].

Over the past decade, several agents targeting mitochondria in cancer cells have entered clinical trials to evaluate their efficacy, safety, dosage, and pharmacokinetic profiles. Anticancer agents that directly target mitochondrial transmembrane potential, respiration, membrane permeability, and mtDNA, or that functionally affect the metabolic alterations associated with mitochondrial dysfunction in various cancer types, along with their mechanisms of action, effects, and clinical trial statuses, have been comprehensively reviewed by Wang's and Shrestha's groups [113, 114]. Here, we provide a concise summary of recent advancements in clinical trials involving approved pharmaceuticals targeting mitochondria for cancer treatment. The lipoate derivative CPI-613 is the first anticancer agent that selectively and strongly disrupts mitochondrial metabolism, inducing apoptosis in multiple cancer types with low toxicity [115]. In phase I trial as a single agent (NCT01034475), no dose-limiting toxicities were observed when 26 patients with advanced hematologic malignancies received a 2-hour infusion of CPI- 613 at doses up to 2,940 mg/m^2 six time within 28 days. The clinical benefit rate was 29% among the 21 evaluable patients [116]. In another phase I trial (NCT01835041), the maximum dose of CPI- 613 was assessed in combination with modified FOLFIRINOX chemotherapy, which includes oxaliplatin, leucovorin, irinotecan, and fluorouracil, in 20 patients with metastatic pancreatic cancer. The maximum tolerated dose of CPI- 613 was determined to be 500 mg/m^2 per day, and 11 out of 18 evaluable patients (61%) achieved who received this dose achieved a complete or

partial response. While there were some unexpected hematological and non-hematological adverse events, no deaths were reported as a result of these events [117]. Additionally, a phase Ib multicenter clinical trial (NCT04203160) involving 20 patients with advanced biliary tract cancer demonstrated that a combination of CPI- 613 at a higher dose (2,000 mg/m^2 over 2 hours) with gemcitabine and cisplatin is well tolerated and shows a promising synergistic effect by significantly decreasing mitochondrial respiration [118]. Zotiraciclib (TG02) is pyrimidine-based multikinase inhibitor known for its ability to penetration the blood-brain barrier. It has been reported to induce apoptosis and necrosis in glioblastoma cells both in vitro and in vivo by causing mitochondrial dysfunction and suppressing glycolysis, ultimately inhibiting ATP depletion production [119]. In a phase I trial (NCT02933944), the cancer vaccine TG02, in combination with the adjuvant GM-CSF, was administrated to 6 patients with locally advanced primary and recurrent RAS mutant CRC. The results demonstrated that this combination therapy was well tolerated and induced a high level of systemic immune response in 4 patients. However, the small sample size limits the ability to draw definitive clinical outcome reporting, such as assessing the killing efficacy [120]. Mitochondrially targeted tamoxifen (MitoTam), a novel inhibitor of respiratory complex I, is a first-in-class mitochondrially targeted anticancer drug that preferentially accumulates in the mitochondria and disrupts the respiratory chain and energy production of cancer cells. A phase I/Ib clinical trial (EudraCT number 2017–004441- 25) in patients with metastatic solid tumors showed that MitoTam exhibited manageable safety profile when administrated at a dose of 3.0 mg/kg once per week, and achieved the greatest clinical benefit rate (83%) and a long-term therapeutic effect in patients with metastatic renal cell carcinoma, and there was a significant loss of active mitochondria and reduction in mitochondrial network in enriched circulating tumor cells after the treatment [121, 122]. Banxiaxiexin decoction has been widely used in Traditional Chinese Medicine for the treatment of digestive diseases for over 1,800 years in China. Recently, a randomized controlled trial involving 146 patients with GC demonstrated that combining Banxiaxiexin decoction with chemotherapy improved overall survival, progression free survival, tumor immune surveillance, and clinical symptoms by promoting the mitochondria-mediated apoptosis pathway. Additionally, it alleviated certain adverse reactions, indicating this decoction benefited the chemotherapy for GC clinically [123]. Taken together, these clinical trials offer more first-line treatment options for patients with advanced cancers.

Studies on agents targeting both Wnt signaling and mitochondria in cancers

Currently, several anticancer agents capable of inducing mitochondrial dysfunction through the inhibition in canonical Wnt signaling have been identified. The selective phosphodiesterase type 4 inhibitor Zl-n- 91, known for its high selectivity and minimal side effects, mediates mitochondrial dysfunction by inhibiting canonical Wnt signaling in acute myeloid leukemia (AML) cells. This action reduces malignant cell proliferation and demonstrates notable anticancer effects [124]. Additionally, Zl-n- 91 exhibits strong neuroprotective activity, making it a promising candidate for AML treatment, although its specific mechanisms require further investigation. Exploring new anti-cancer active ingredients from natural products and modifying their structures is also an effective strategy for novel drug development. For instance, HcBPS2, a polysaccharide extracted from daylily, has been demonstrated to inhibit overactivated canonical Wnt signaling in malignant HCC. Mechanistically, it increases the protein levels of proapoptotic CYC and Bax in cancer cells, decreases the protein level of antiapoptotic Bcl- 2, and activates caspase- 9/3, thereby initiating caspase-dependent apoptosis [71]. PAB exhibits antifungal, antifertility, and anti-angiogenic effects, along with broad-spectrum antitumor activity. Guan et al.. discovered that PAB exerts anticancer effects on cervical cancer by blocking canonical Wnt signaling to downregulate PAX2, inducing mitochondrial apoptosis, and increasing mitochondrial outer membrane permeability through upregulation of Bax expression. This positions PAB as a potential therapeutic agent for cervical cancer treatment [74]. Mitochondrial-processing peptidase subunit beta (PMPCB) plays a crucial role in mitochondrial protein processing and maintaining mitochondrial homeostasis. Interestingly, EpCAM-positive HCC cells, a CSC-like HCC subtype associated with poor prognosis, rely on PMPCB to sustain stemness. PMPCB also activates canonical Wnt signaling by promoting FOXOs phosphorylation, nuclear translocation, and interaction with β-catenin. Consequently, PMPCB silencing induces significant apoptosis and tumor suppression in HCC and breast cancer by effectively inhibiting EpCAM expression and canonical Wnt signaling, primarily through a marked reduction in mitochondrial respiration and ATP levels, along with increased ROS levels [125]. This finding suggests that PMPCB is a promising synthetic lethal candidate for personalized cancer treatment by targeting both canonical Wnt signaling and mitochondrial function. Recently, a study demonstrated that exosomal miR- 484 derived from human bone marrow mesenchymal stems, which is decreased in pancreatic cancer cells, inhibits the growth of these cells and induces apoptosis both in vitro and in vivo

by deactivating canonical Wnt signaling and suppressing mitochondrial function and related energy metabolism. The addition of LiCl, a classical activator of canonical Wnt signaling, can restore the disrupted mitochondrial metabolism. These results suggest that activated canonical Wnt signaling promotes pancreatic carcinogenesis by upregulating mitochondrial function and metabolism, which can be mitigated by the overexpression of exosomal miR- 484 derived from human bone marrow mesenchymal stems [126]. Additionally, when curcumin, a dual inhibitor of canonical Wnt and androgen receptor signaling, is encapsulated in calcium-doped dendritic mesoporous silica nanoparticles modified with folic acid, it demonstrates better biocompatibility and greater efficacy compares to free curcumin. This formulation also enhances cell cycle arrest and increases apoptosis rate in breast cancer cells both in vitro and in vivo by inhibiting canonical Wnt signaling, disrupting mitochondrial membrane potential, and activating mitochondria-mediated apoptosis pathway [127]. These findings suggest that this anticancer drug formulation holds significant potential for breast cancer treatment.

Although the aforementioned agents show promising therapeutic potential in cancer management, and theoretically, all agents targeting canonical Wnt signaling could influence mitochondrial processes, few strategies or agents have been reported to target both canonical Wnt signaling and mitochondria simultaneously. Importantly, the pathogenesis of cancer is a complex and multifaceted process that cannot be elucidated by a single pathogenesis. Wnt signaling pathways also exhibit variations in activation and inhibition across different cancer types. For instance, canonical Wnt signaling is frequently overactivated in CRC, initiating the expression of numerous genes related to CSC properties and development, thereby sustaining CSCs survival and facilitating malignant cancer progression [128]. In breast cancer, alterations in the Wnt signaling pathways are more intricate. In TNBC and basal-like breast cancer, the expression of most Wnt receptors is abnormally elevated, resulting in the overactivation of both canonical and noncanonical Wnt signaling pathways [129]. Conversely, activation of the noncanonical Wnt pathway mediated by Wnt5a inhibits breast tumor metastasis by impairing cell migration and invasion [130]. However, during melanoma metastasis, the Wnt5a-mediated noncanonical Wnt pathway promotes cytoskeletal rearrangement, enhancing cancer cell migration and invasion [131]. In general, most studies support the carcinogenic role of canonical Wnt signaling in the occurrence and development of cancer, suggesting that inhibition of this cascade may be beneficial for treating most types of cancer. Conversely, noncanonical Wnt signaling may play an opposing role in this pathogenesis, likely due to its more complicated molecular regulatory network, which requires further in-depth study. Mitochondrial alterations and functions also differ significantly among various cancer types. In lung adenocarcinoma, increased mtDNA levels and mitochondrial respiration exacerbate tumor burden, elevated levels or activity of Drp1 also promote mitochondrial fission, which transports smaller mitochondria to the cell periphery and increases local ATP generation, thereby promoting cancer cell migration and metastasis [132, 133]. However, normal osteocytes transfer mitochondria to cancer cells, increasing mtDNA levels in the cytoplasm of cancer cells, activating antitumor immune responses to inhibit bone metastasis [134]. In primary GC patients, the number and function of mitochondria in peripheral blood mononuclear cells are downregulated, and mitochondrial membrane potential levels are reduced, leading to elevated mitochondrial ROS levels and inducing apoptosis of immune cells, ultimately weakening the patient's antitumor immune response [135]. Although mitochondrial content and function are abnormal in most cancer types, a recent meta-analysis indicates that changes in mtDNA copy number are only associated with the risk of lip, oral, and testicular cancers among common cancer types [136]. These differences underscore the diversity in cancer mechanisms, with distinct alterations in cellular metabolism and signal transduction across cancer types. Regulating the function of a single signaling pathway or organelle is therefore insufficient to cure cancer. The most viable option may be combination therapy, incorporating canonical Wnt signaling-based inhibitors, mitochondria-based agents and conventional therapies such as chemoradiotherapy, targeted therapy and immunotherapy. However, it is crucial to accurately identify and quantify the changes of specific components responsible for the dysfunction of Wnt signaling pathways and mitochondria within particular cancer type and their tumor microenvironment. Fortunately, the development and gradual popularization of molecular diagnostic technologies, such as multi-omics sequencing in clinical practice, will inevitably facilitate personalized cancer treatment through targeted therapeutic strategies based on precise diagnosis.

Summary and prospect

There is mounting evidence indicating that mitochondria play a pivotal role in the pathogenesis and progression of cancer. Given the substantial energy requirements and the hypoxic conditions within the tumor microenvironment, cancer cells predominately rely on aerobic glycolysis as their primary energy-generating pathway. This pathway not only meets the high energy demands but also contributes to the formation of the tumor microenvironment, thereby promoting the progression of cancer. However, reduced levels

Table 1 The regulatory effect of Wnt signaling pathways on mitochondria and related mechanisms in cancer

Components in Wnt signaling	mitochondria -related components	Effect on mitochondria	Effect on cancer	Mechanisms	Reference
LATS2	Drp1	Promote mitochondrial fission	Inhibits the viability of HCC cells	LATS2 regulates Drp1 expression by activating the canonical Wnt signaling, thus to promote mitochondrial fission.	[44]
PDK1	PDH	Inhibit TCA cycle	Accelerates cancer progression of CRC	PDK1 inhibits the conversion of pyruvate to acetyl-CoA by phosphorylating PDH complex, allowing more pyruvate to be converted into lactate.	[47, 52]
c-Myc	PKM2, Glut1	Inhibit TCA cycle-dependent energy supply	Increases aerobic glycolysis in KRAS mutant CRC cells	Canonical Wnt signaling-induced c-Myc overexpression upregulates PKM2 and Glut1 expression, resulting in a major activation of the Warburg effect.	[53]
Wnt5b/c-Myc	MCL1	Reduces mitochondrial mass and OXPHOS	Inhibits mitochondria-dependent apoptosis of TNBC cells	Canonical Wnt5b signaling upregulates c-Myc expression, which in turn activates MCL1 transcription and inhibits mitochondria-dependent apoptosis by binding to the antiapoptotic BCL2.	[76]
LRP5	Glut1, HK2, LDHA, PKM2, HIF1α	Reduces mitochondrial mass	Enhances the malignant phenotypes and drug resistance of GC cells	LRP5 activates the canonical Wnt signaling and promotes aerobic glycolysis by upregulating the expression genes related to aerobic glycolysis.	[54]
β-catenin	PGC1α, TFAM, NRF1	Increases mitochondrial mass	No data	β-catenin knockdown leads to downregulation of proteins related to carbohydrate metabolism and TCA cycle, and promotes lipid metabolism	[64]
PAX2	Bax	Inhibit the expression of proapoptotic Bax in mitochondria	Inhibits mitochondria-dependent apoptosis of cervical cancer cells	The activation of PAX2/Wnt/antiapoptotic axis inhibits the apoptosis of cancer cells by downregulating Bax expression.	[74]

of oxidative phosphorylation levels within the mitochondria of cancer cells does not imply mitochondrial dysfunction. Instead, mitochondria aid cancer cells in evading apoptosis by adjusting the concentrations of various oxidative phosphorylation metabolites, posing a formidable challenge to cancer therapy. Moreover, the Wnt signaling pathways, among the most conserved signaling pathways, have been extensively studied, yet the interaction and molecular mechanisms between Wnt signaling and mitochondria remain largely unexplored. This review systematically delineates how the Wnt signaling pathways, particularly the canonical Wnt signaling, influences cancer initiation and progression through the regulation of mitochondrial dynamics, mitochondrial respiration and metabolism, and mitochondrial-dependent apoptosis (Table 1). Additionally, various agents targeting the canonical Wnt signaling and mitochondria, each with distinct pharmacological mechanisms, have been identified, and despite being in the experimental phase and clinical trial, they have shown varying degrees of efficacy across most cancer types. Consequently, precise molecular diagnostics to determine the involvement of Wnt signaling pathways and mitochondrial factors in cancer development, in conjunction with the selection of targeted therapies and integration with conventional cancer treatments, hold promise for personalized cancer care.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval Not applicable.

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