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MINIREVIEW

# WNT Signaling: an Emerging Mediator of Cancer Cell Metabolism?

**Victoria Sherwood**

Division of Cancer Sciences, Medical Research Institute, Ninewells Hospital and Medical School, University of Dundee, Dundee, United Kingdom

**WNT signaling was discovered in tumor models and has been recognized as a regulator of cancer development and progression for over 3 decades. Recent work has highlighted a critical role for WNT signaling in the metabolic homeostasis of mammals, where its misregulation has been heavily implicated in diabetes. While the majority of WNT metabolism research has focused on nontransformed tissues, the role of WNT in cancer metabolism remains underinvestigated. Cancer is also a metabolic disease where oncogenic signaling pathways regulate energy production and macromolecular synthesis to fuel rapidly proliferating tumors. This review highlights the emerging evidence for WNT signaling in the reprogramming of cancer cell metabolism and examines the role of these signaling pathways as mediators of tumor bioenergetics.**

Following the initial discovery of WNT1 in a murine breast cancer model in the early 1980s (1), 19 WNT genes have been identified in mammals. All of these genes encode secreted glycoproteins that signal through an array of receptors and coreceptors to elicit control over cell proliferation, stem cell self-renewal, and cellular differentiation in a variety of tissues. WNT ligands can signal via a number of pathways, which can be broadly subdivided into two categories based on whether or not they signal through an intracellular transcriptional coactivator called β-catenin. The WNT/β-catenin pathway is commonly referred to as the canonical WNT pathway, whereas the noncanonical pathway is an umbrella term for β-catenin-independent WNT signaling. In recent years, the WNT/β-catenin signaling pathway has been found to be involved in the development of diabetes mellitus and obesity. A number of genome-wide association studies and genetically engineered animal models have identified components of the WNT/β-catenin pathway in susceptibility to obesity and diabetes, in addition to the WNT ligands themselves (2–6). The majority of the genes that are associated with susceptibility to type 2 diabetes regulate β-cell function. Loss of β-catenin in the adult murine pancreas leads to glucose intolerance and protection from high-fat-diet-induced obesity and insulin resistance (7). Furthermore, WNT signaling is also strongly implicated in the control of adipose tissue to systemically regulate glucose homeostasis and adipogenesis during obesity (8–11). These findings highlight that the WNT/β-catenin signaling pathway regulates whole-body metabolism in mammals by altering the behavior of multiple cell types and tissues involved in growth, insulin secretion, and energy expenditure.

Although hormones and other extracellular signaling components facilitate metabolic communication between tissues and organs, at the cellular level, the expression of specific enzyme isoforms and regulatory molecules allows for localized, tissue-specific regulation of metabolism to support specialized cellular functions. Recently, evidence has emerged that highlights a role for WNT-mediated regulation of cellular metabolism as well, including the reprogramming of tumor cell bioenergetics (12–15). This review explores the evidence that components of the WNT signaling pathways regulate cellular metabolism with a specific focus on cancer cells. Furthermore, I explore whether this regulation is controlled either through direct interplay of these components with the cellular metabolism machinery or through cross talk with other oncogenic pathways that are already well-established regulators of tumor cell metabolism. Although our current understanding of the molecular mechanisms involved in this regulation are still incomplete, this work highlights a whole area of WNT signaling that up until now has been poorly investigated, with an aim to emphasize some of the most interesting opportunities for future research efforts.

## WNT SIGNALING PATHWAYS

**Canonical WNT signaling.** WNT signaling pathways regulate a myriad of biological functions in animals through embryonic development and in adult tissues (16). The canonical WNT pathway involves activation of the key effector molecule β-catenin. In this signaling pathway, β-catenin functions as part of a bipartite transcription factor that activates WNT target genes by interacting with other transcription factors, classically, those belonging to the T cell factor/lymphoid-enhanced binding factor 1 (TCF/LEF1) family (Fig. 1). The WNT/β-catenin pathway has been well defined by numerous studies showing that WNT receptor interaction results in the stabilization of a cytosolic pool of β-catenin by inactivating the anchoring axin-adenomatosis polyposis coli (APC) complex, which is essential for the function of a β-catenin destruction complex. In the absence of an extracellular WNT signal, β-catenin is anchored by the axin-APC complex, subsequently phosphorylated by casein kinase Iα (CKIα) and glycogen synthase kinase 3β (GSK3β), and then ubiquitinated by the SKP1–cullin1–F-box (SCF-β-TRCP) E3 ubiquitin ligase, leading to 26S proteasome-mediated degradation. Upon WNT binding to the frizzled (FZD) and LRP5/6 coreceptors, the axin-APC destruction complex is inactivated through recruitment of the intracellular signaling protein dishevelled (DVL), which prevents β-catenin degradation and allows nuclear translocation of the stabilized pool to activate gene transcription (Fig. 1) (17, 18). WNT signaling is antagonized by a number of endogenous mechanisms, two of which involve the secretion of WNT activity inhibitors, i.e.,

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Address correspondence to v.sherwood@dundee.ac.uk.

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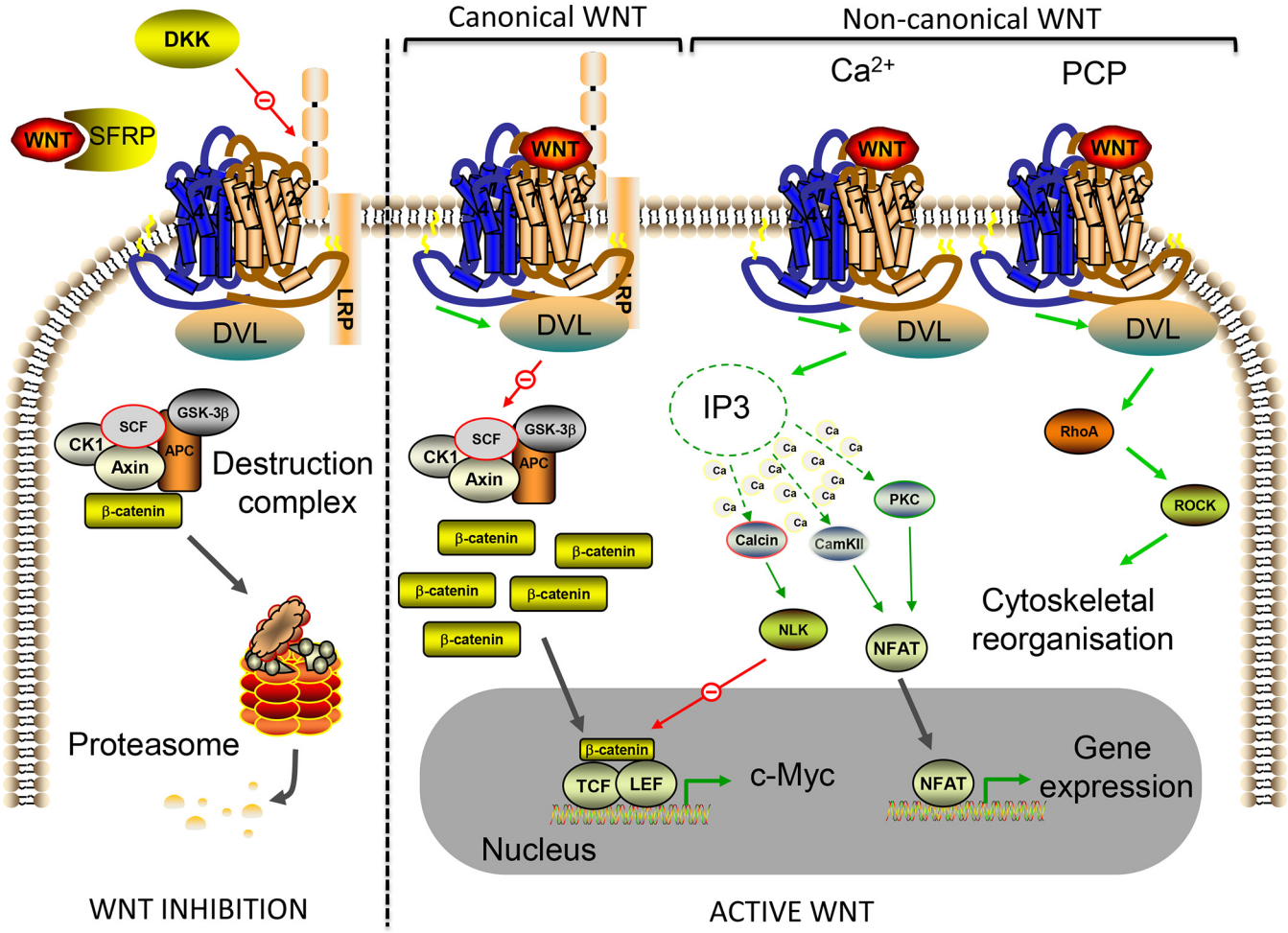


**FIG 1** Overview of the WNT signaling network. WNT ligands signal via a number of intracellular pathways in a highly tissue context-dependent manner. In the "off" state, WNT signaling is inhibited (left of the broken line). Extracellularly, this occurs through secreted frizzled receptor-related protein (SFRP) sequestering of WNT ligands to inhibit both canonical (β-catenin-dependent) and noncanonical (β-catenin-independent) WNT signaling. Dickkopf (DKK) is an extracellular antagonist of the LRP5/6 receptor, which is specific to the canonical WNT pathway. For the canonical pathway, in the absence of a WNT ligand, β-catenin levels in the cell are kept low (except at adherens junctions, where β-catenin exists in a cadherin-bound pool at the cell membrane) by a multiprotein destruction complex. The destruction complex binds and phosphorylates β-catenin, targeting it for polyubiquitination and proteasome-mediated degradation. In the presence of WNT ligands, the signaling network becomes activated (right of the broken line). In the canonical WNT pathway, WNT ligands bind to the FZD receptors (large seven-transmembrane domain receptors; blue/brown in schematic) and LRP5/6 coreceptors to activate DVL. DVL inactivates the destruction complex, which in reality occurs through recruitment of the scaffold protein axin to the cytoplasmic tail of LRP5/6, preventing β-catenin degradation. Following inactivation of the destruction complex, cytoplasmic levels of β-catenin rise and the protein is eventually translocated to the nucleus, where it associates with TCF/LEF transcription factors to control the expression of WNT target genes such as the c-Myc gene. Noncanonical WNT signaling consists of two main pathways, the WNT/$Ca^{2+}$ and WNT/PCP pathways. Both of these pathways involve WNT ligand binding of FZD receptors (also involving coreceptors; not shown) and subsequent activation of DVL. In the WNT/$Ca^{2+}$ pathway, intracellular $Ca^{2+}$ levels increase following WNT-induced activation of phospholipase C, resulting in inositol 1,4,5-triphosphate-3 (IP3) generation and subsequent $Ca^{2+}$ release from intracellular stores. Increased $Ca^{2+}$ levels result in activation of $Ca^{2+}$-dependent enzymes and subsequent NFAT-mediated gene activation and inhibition of TCF gene transcription through activated NLK. The WNT/PCP pathway involves WNT-mediated activation of the small GTPase RhoA, which activates Rho-associated kinase (ROCK) to remodel the cytoskeleton and regulate cell movement and tissue polarity. Red arrows represent inhibition, green arrows represent activation, gray arrows represent translocation, and broken green arrows represent second-messenger signaling. See the text for additional details.

secreted frizzled receptor-related proteins (SFRPs) and dickkopf proteins (DKKs) that function as LRP and FZD decoys, respectively (19).

Although the mechanistic understanding of WNT/β-catenin signaling has been the subject of intense investigation, we are still learning about the complex and often context-dependent effects of WNT signaling in disease progression, such as in cancer. WNT signaling and its numerous downstream effectors regulate a number of biological processes associated with carcinogenesis, including tumor formation, proliferation, cell death, senescence, cell differentiation, metastasis, and more recently (as reviewed here) also in tumor metabolism. Components of the WNT/β-catenin pathway are frequently mutated in tumors, highlighting the importance of this pathway in the oncogenic process. One of the best examples is the loss of functional APC expression in colorectal cancer (CRC) patients, where APC mutations mimic active WNT/β-catenin signaling and are associated with initiation of CRC (20). Other colorectal tumors and types of cancer (including lung can-

cer, hepatocarcinoma, medulloblastoma, ovarian cancer, and breast cancer) can also exhibit loss of functional axin or other mutations that stabilize β-catenin expression (21–26). These findings have prompted researchers to develop inhibitors of the WNT/β-catenin signaling pathway for therapeutic use to treat cancer, although the vast majority of these are still at the preclinical testing stage (27). The use of such therapeutics in cancer treatment is, however, confounded by the response of specific tumor types to WNT/β-catenin signaling. In some cancers, for example, melanoma and prostate cancer, patients with higher levels of active β-catenin signaling possess improved predicted outcomes (28, 29). This highlights the need for a better understanding of the context-dependent nature of WNT signaling in cancer.

**Noncanonical WNT signaling.** Noncanonical WNT signaling is a collective term for a number of β-catenin-independent pathways that are composed of different types of ligands and receptors. Noncanonical WNT signals are transduced either through intracellular $Ca^{2+}$ levels or by small GTPases that regulate cytoskeletal remodeling; these are referred to as the $Ca^{2+}$ and planar cell polarity (PCP) pathways, respectively (Fig. 1). We have known for over a decade now that Wnt ligands are able to induce the release of intracellular $Ca^{2+}$ to activate $Ca^{2+}$-dependent enzymes such as phosphatase, calcineurin (Calcin), protein kinase C (PKC), and calmodulin-dependent kinase II (CamKII) (30–32) to mediate diverse effects in animal tissues. PKC and CamKII control dorsoventral patterning in embryos (32, 33) through modulation of cell adhesion, migration, and differentiation, which are regulated by the transcription factor nuclear factor of activated T cells (NFAT) (34, 35). Calcineurin, on the other hand, activates nemo-like kinase (NLK) to phosphorylate TCF transcription factors and antagonize canonical WNT signaling (36). Unlike the WNT/$Ca^{2+}$ pathway, the WNT/PCP pathway is not directly involved in transcriptional regulation, but rather, FZD activation leads to increased Rac and Rho small GTPase activity that results in cytoskeletal reorganization and changes to cell polarity and migration (37, 38). Of the noncanonical pathways, it is the WNT/$Ca^{2+}$ signaling pathway that has been most strongly associated with tumor formation and progression. The most common WNT ligand that has been found to activate WNT/$Ca^{2+}$ signaling in cancer cells is WNT5A, and its expression is associated with both tumor-suppressive and pro-oncogenic roles, depending on the tumor type. For example, enhanced WNT5A expression correlates with a good patient prognosis in breast and colon cancers (39, 40) yet poor survival in melanoma and gastric cancer (41, 42), again highlighting the context-dependent nature of WNT signaling in carcinogenesis.

## WNT SIGNALING CROSS TALK

The concept that the WNT signaling pathways, as presented above, function as autonomous signal transduction processes has been replaced in the field with an understanding that, rather, the pathways function as a network of integrated WNT signaling activities. A plethora of evidence now exists showing that WNT ligands and their downstream signaling components are involved in more than one of the pathways, that the pathways regulate many of the same biological processes, and that within tissues the pathways regulate one another, which, taken together, demonstrates that the WNT proteins activate a signaling network (43, 44). Here I explore how this WNT signaling network regulates tumor cell metabolism and, for clarity, provide examples based on the individual WNT signaling pathways, canonical and noncanonical.

## WNT AND NORMAL CELL METABOLISM

Carbohydrate metabolism is central to energy generation in cells, and for well over a century, biochemists have worked on generating detailed maps of central carbon metabolism, highlighting the substrates, enzymes, cofactors, and metabolites involved in these biochemical reactions. There are several core metabolic pathways involved, including glycolysis, the pentose phosphate pathway (PPP), the tricarboxylic acid (TCA) cycle, and the electron transport chain (ETC). Glucose is a key substrate, where it can be converted to the nucleotide component ribose-5-phosphate and NADPH by the PPP or oxidized in glycolysis to convert it into pyruvate and generate ATP. In normal cells, the fate of pyruvate is determined by $O_2$ availability; in normoxia, pyruvate is further degraded to form acetyl coenzyme A (acetyl-CoA), which can be used by the TCA cycle and ETC to generate more ATP through oxidative phosphorylation (OXPHOS). In hypoxia, however, pyruvate is converted to the waste product lactic acid by the enzyme lactate dehydrogenase (LDH) and removed from the cell. It is now understood that determining how the flow of metabolites through metabolic networks is regulated will be essential in determining where best to apply therapeutic interventions to treat metabolic disorders (45), and in recent years, there has been a surge in uncovering new mechanisms of metabolic regulation. One such regulator that has been discovered is the WNT signaling network.

WNT signaling is now known to effect cellular metabolism in normal cell types, which has been the subject of a previous excellent review (46). For example, in fibroblasts and myoblasts, active WNT3A/β-catenin signaling enhances mitochondrial biogenesis and $O_2$ consumption (47). Furthermore, the WNT repressor SFRP-5 has been shown to suppress oxidative metabolism in adipocytes through inhibition of WNT3A activity (8). In contrast, a recent study showed that WNT3A signaling in a noncanonical manner (i.e., independent of axin, GSK3β, and β-catenin) increased glycolytic activity during osteoblast differentiation (48). These studies provide direct evidence of the context-dependent nature of WNT signaling in regulating glucose metabolism, at least in normal cells, and raises the question of whether WNT signaling can also control cancer cell metabolism, where well-characterized perturbed metabolic processes exist to facilitate tumor growth.

## CANCER CELL METABOLISM

It has long been known that cellular metabolism in tumors is vastly different from that in normal tissues (Fig. 2). For example, in the first half of the last century, the German biochemist Otto Warburg observed that cancer cells exhibit aerobic glycolysis (elevated glycolysis even in normoxia) (49), which facilitates high levels of biosynthetic fluxes during rapid proliferation, resulting in increased glucose consumption and lactate secretion (50). This metabolic shift away from mitochondrion-dependent energy production toward anoxic breakdown of glucose involves the coordinated upregulation of glucose transporters and glycolysis enzymes by oncogenes, such as c-Myc and protein kinase B (Akt). Another crucial metabolic adaptation of cancer cells is glutaminolysis, where the anaplerotic flux of glutamine catabolism to α-ketoglutarate, as a carbon source for the TCA cycle, facilitates amino acid, nucleotide, and lipid synthesis (51). c-Myc has been shown to be a

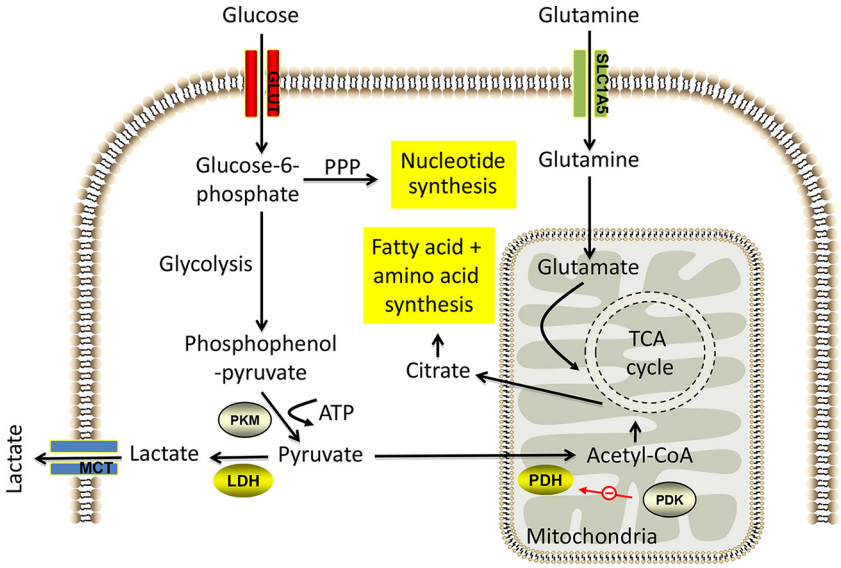


**FIG 2** Summary of metabolic pathways in cancer cells. Highly proliferative cells upregulate key metabolic pathways to facilitate glucose catabolism and glutamine catabolism, which are interlinked to drive macromolecular synthesis and maintain energy balance. Cancer cells use aerobic glycolysis (left side) to produce ATP (two molecules for every molecule of glucose), which is promoted by increased expression of glycolytic enzymes such as pyruvate kinase isozymes M1/M2 (PKM) and LDH. Secretion of the accumulated lactate is achieved by the monocarboxylate transporter (MCT). Furthermore, oncogene-driven pyruvate dehydrogenase kinase (PDK) expression inhibits pyruvate dehydrogenase (PDH) to prevent TCA cycle flux and promote glycolysis. The PPP is parallel to glycolysis and generates NADPH and five-C sugars. Glutaminolysis (right side) is the metabolic process by which glutamine is deaminated to form glutamate and subsequently α-ketoglutarate to maintain the TCA cycle. Glutamine is taken up into the cell by amino acid transporters such as the SLC1A5 transporter. Glucose-derived citrate from the TCA cycle is exported to the cytosol, where it is further converted to acetyl-CoA for lipid synthesis or to oxaloacetate for amino acid synthesis. See the text for additional details.

key regulator of glutaminolysis in tumors (52, 53). In addition, many tumors also exhibit a lipogenic phenotype by upregulating enzymes that facilitate *de novo* fatty acid synthesis required for biological membrane production (54). Intensive research in recent years has endeavored to determine how the metabolic activity of tumors is regulated, and as a result of this work, evidence has emerged that the WNT signaling pathways represent regulatory mediators of the perturbed metabolic activities of cancer cells.

## CANONICAL WNT SIGNALING AND CANCER CELL METABOLISM

There is an ever-increasing body of evidence demonstrating that WNT/β-catenin signaling regulates cellular metabolism in tumors. Early observations drew speculative links, as it was demonstrated more than a decade ago in ovarian cancer that a large number of metabolism genes were found to be β-catenin–TCF transcriptional targets, including enzymes involved in glutamine and fatty acid metabolism (55). However, more recently, direct associations have been demonstrated for control of cancer cell metabolism by the canonical WNT pathway. In breast cancer, for example, WNT/β-catenin signaling increases aerobic glycolysis through suppression of mitochondrial respiration by reducing the transcription of the gene for cytochrome *c* oxidase, which is an integral enzyme of the ETC and thus essential for OXPHOS (12). Furthermore, in triple-negative breast cancer cells, WNT5B was recently shown to be able to control the expression of the OXPHOS-related genes for cytochrome $c_1$ and the ATP synthase γ subunit through the canonical WNT pathway (15). In CRC too, an elegant study recently showed that canonical WNT signaling promotes aerobic glycolysis though increased expression of pyruvate dehydrogenase kinase 1 (PDK1), an enzyme that inhibits mitochondrion-bound pyruvate dehydrogenase (PDH) to decrease pyruvate oxidation, resulting in increased pyruvate conversion to lactate in the cytosol (Fig. 2) (14). Furthermore, the lactate transporter monocarboxylate transporter 1 (MCT-1) is also upregulated, facilitating lactate secretion, where this enhanced secretion was shown to have microenvironmental effects in tumor tissue by promoting angiogenesis (14). This suggests that the WNT/β-catenin-mediated metabolic reprogramming of cancer cells can directly affect vessel density in tumors. In fact, in other models, canonical WNT signaling has been strongly linked to tumor angiogenesis by directly regulating the expression of the proangiogenic growth factor (GF) vascular endothelial GF (56–58). Since blood vessels deliver nutrients and $O_2$ to tissues, it is hardly surprising that metabolism and angiogenesis should be coregulated by WNT signaling. Such work has identified a key role for WNT/β-catenin signaling in the regulation of cancer cell metabolism, but how this regulation is controlled is still poorly understood and likely to be highly context dependent. Here I outline important functions of WNT/β-catenin signaling that play a role in the metabolic regulation of tumors, highlighting opportunities for future investigations. These functions include control of c-Myc expression, concomitant regulation of the WNT signaling pathways themselves by metabolic enzymes and nutrients, and cross talk with reactive oxygen species (ROS) signaling.

The c-Myc gene is a well-characterized proto-oncogene that is transcriptionally activated by canonical WNT signaling. c-Myc functions as a transcription factor by binding enhancer box sequences (CACGTG) of target genes to regulate the expression of a number of genes, many of which were historically found to be involved in cell cycle control, including those for cyclins, cyclin-

dependent kinases (CDKs), and CDK inhibitors (59–62). Crucially c-Myc-mediated transcriptional changes also promote glycolysis and energy production in transformed cells (63). It is well established that WNT/β-catenin signaling transcriptionally upregulates c-Myc expression in a TCF-dependent manner (64, 65) and through an elegant study investigating a simultaneous conditional knockout of APC and c-Myc in intestinal crypts, c-Myc expression was demonstrated to be essential for the oncogenic potential of canonical WNT signaling in CRC (66). Furthermore, the WNT signaling pathway is also downstream of c-Myc through transcriptional repression of the secreted Wnt inhibitors DKK1 and SFRP-1 in cancer cells (67). This provides a positive feedback loop between WNT and c-Myc signaling, placing c-Myc as a key oncogenic component of the WNT/β-catenin signaling pathway. Myc regulates gene transcription in growing cells, where it actively controls a myriad of metabolic processes to facilitate growth and proliferation, which has been the subject of a recent review (68). Glycolysis, nucleotide synthesis, lipid synthesis, glutaminolysis, and mitochondrial bioenergetics are all controlled by Myc-driven transcriptional regulation in cancer cells, all of which are essential for biomass accumulation and genome replication in rapidly dividing cells (50, 68). Specifically, c-Myc promotes the metabolic reprogramming of cancer cells during the $G_1$ phase of the cell cycle, inducing ROS production and activating master transcriptional regulators of cellular metabolism such as the forkhead transcription factors (FOXOs), while also promoting autophagy (69). Cross talk between the WNT and c-Myc pathways in cancer cells means that they converge to regulate not only progression through the cell cycle but also concomitant reprogramming of tumor cell metabolism. Important evidence of this is that β-catenin-mediated c-Myc expression results in upregulation in the expression of a number of rate-limiting glycolytic genes, including those for glucose transporter 1 (GLUT-1), LDH, and the M2 isoform of pyruvate kinase (PKM2; the enzyme that catalyzes the final step of glycolysis to produce ATP and pyruvate) to promote aerobic glycolysis in cancer cells (70).

Aside from aerobic glycolysis, c-Myc also induces glutaminolysis through induction of the solute carrier family 1 member 5 (SLC1A5) glutamine transporter and the mitochondrial glutaminase enzyme to increase glutamine uptake and its subsequent conversion to glutamate, respectively (53). Recently, β-catenin was shown to stimulate c-Myc-mediated glutamine metabolism in colon cancer cells (71). As recently suggested, canonical WNT stimulation of c-Myc provides cancer cells with the concomitant simulation of glutaminolysis and glycolysis to support increased nucleotide and fatty acid synthesis, thus driving *de novo* biosynthesis during proliferation (72). Therefore, transcriptional upregulation of c-Myc is a key component of canonical WNT-mediated metabolic reprogramming of cancer cell metabolism (Fig. 3).

Metabolic enzymes, by-products, and nutrients have all been shown to regulate canonical WNT signaling, suggesting that the WNT/β-catenin pathway represents a newly discovered signaling node that can detect environmental changes in nutrient and $O_2$ availability to subsequently control metabolic reprogramming events through gene expression changes in cancer cells. The glycolysis enzyme PKM2 is a pleiotropic protein and can also function as a transcriptional coactivator (73, 74). Nuclear translocation of PKM2 facilitates its interaction with β-catenin downstream of epidermal GF (EGF) signaling in a variety of cancer cell types to elicit β-catenin-induced transcriptional changes, resulting in c-Myc expression and subsequent upregulation in GLUT-1 and LDH (70, 73, 75). However, there is cross talk between the canonical WNT and EGF signaling pathways, as EGF–PKM2–β-catenin signaling resulted in increased expression of DKK-1 and hence suppression of canonical WNT signaling under these conditions (73). Another pivotal respiration enzyme, succinate dehydrogenase 5 (an ETC component), has been shown to antagonize β-catenin signaling in lung cancer, resulting in inhibition of transcriptional reprogramming of the WNT/β-catenin-mediated epithelial-to-mesenchymal transition and reduction of tumor metastasis (76). Thus, a number of central cellular metabolism enzymes have been identified as antagonists of canonical WNT signaling in cancer cells, perhaps to suppress potential metabolic reprogramming events.

Mitochondria are an important source of ROS, produced from complexes I and III of the respiratory chain during OXPHOS, as previously reviewed (77). ROS levels in cancer cells can directly affect the transcriptional activity of β-catenin, as ROS has been shown to displace the interaction of β-catenin–TCF4 to facilitate preferential interaction of β-catenin with the FOXO3a transcription factor (78). In breast cancer, shifting β-catenin binding from TCF to FOXO3a altered cell fate from a proliferative, cancer stem cell phenotype to a more differentiated state, reducing pluripotency and tumorigenesis (78). Indeed, oxidative stress can activate canonical WNT signaling in a range of cell types (including neuroblastoma cells) upstream of β-catenin at the level of DVL. DVL interaction with the thioredoxin family protein nucleoredoxin inhibits DVL activity yet can be augmented by $H_2O_2$ treatment, which activates canonical WNT signaling independently of extracellular WNT stimulation (79). Hence, oxidative stress can regulate the canonical WNT pathway to alter transcriptional changes in cancer cells.

In addition to metabolic enzymes and by-products, nutrients have also been shown to regulate β-catenin activity in cancer cells. For example, glucose increases β-catenin acetylation and nuclear accumulation to activate gene expression from WNT target genes in response to simultaneous glucose and WNT ligand stimulation (80). It is logical, then, that nutrient-sensing signaling pathways should regulate canonical WNT signaling, such as AMP-activated protein kinase (AMPK). AMPK is a key energy sensor of intracellular AMP/ATP ratios and can, when AMP is high, inhibit anabolic metabolism while simultaneously activating catabolic pathways such as fatty acid oxidation and glucose metabolism (81). Indeed, activated AMPK can inhibit WNT/β-catenin signaling in cervical cancer cells through reduction of DVL activity (82), suggesting that nutrient sensors can modulate canonical WNT signaling to alter the metabolic reprogramming of cancer cells. Taken together, the above studies have highlighted a variety of mechanisms by which the WNT/β-catenin signaling pathway is integrated into the transcriptional reprogramming of tumor metabolism.

## NONCANONICAL WNT SIGNALING AND CANCER CELL METABOLISM

Until now I have focused on the WNT/β-catenin pathway as a regulator of cancer cell metabolism, yet the noncanonical WNT pathways can also control the metabolic reprogramming of cancer cells, suggesting that the WNT signaling pathways can function as a network in this process. The major mechanism by which the β-catenin-independent WNT pathways regulate cancer cell me-

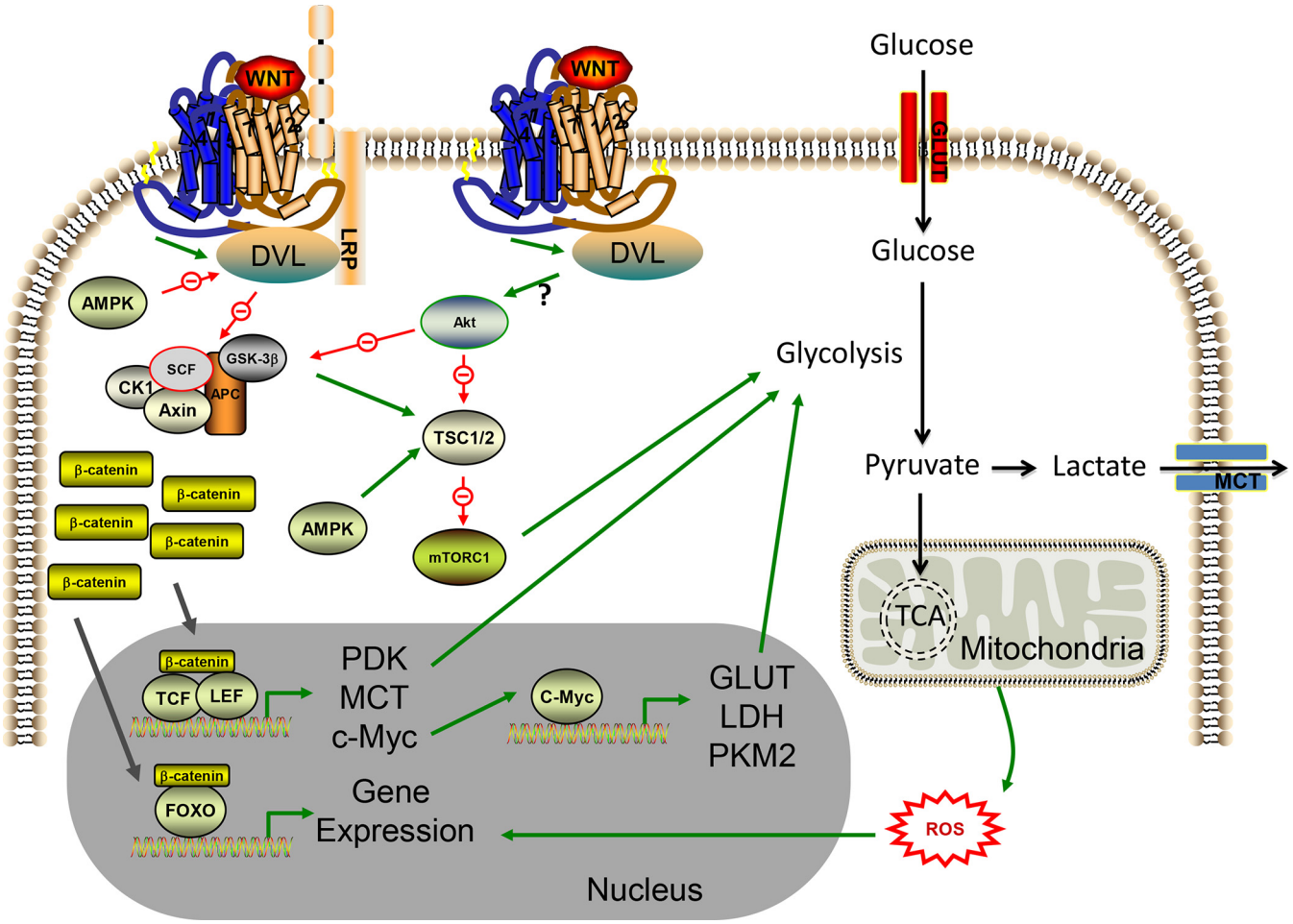


**FIG 3** Effects of the WNT signaling network on cancer cell metabolism. Active WNT signaling is linked to alterations in cancer cell metabolism. Transcriptional changes induced through WNT-mediated stabilization of β-catenin can reprogram cancer cell metabolism, largely by increasing aerobic glycolysis. The pathway can be inhibited by AMPK at the level of DVL activity. β-Catenin–TCF/LEF gene transcription can increase enzymes that promote glycolysis (for example, PDK1, which inhibits pyruvate flux through the TCA cycle) or can increase c-Myc expression. c-Myc induces the transcription of genes for glycolysis enzymes and proteins involved in glutamine catabolism (the latter is not shown). ROS production from the mitochondrial respiratory chain can alter β-catenin fidelity for TCF/LEF and promote binding to FOXO transcription factors. FOXO gene transcription activates genes that combat oxidative stress and therefore promote cell survival. Noncanonical WNT signaling can induce Akt-mTOR activity in cancer cells by a currently undefined mechanism. Stabilization of mTORC1 promotes aerobic glycolysis through a variety of mechanisms, including induction of HIF-1α-mediated transcription of the PKM2 gene (not shown). Cross talk between the WNT/β-catenin and WNT/Akt-mTOR pathways occurs where Akt can inhibit GSK3β, which otherwise, in conjunction with AMPK, could destabilize mTORC1 expression by promoting TSC1/2 activity. This again promotes aerobic glycolysis by stabilizing the expression of both mTORC1 and β-catenin. A question mark indicates that the precise molecular mechanism remains unknown. See the text for additional details.

tabolism is through cross talk with Akt signaling. The Akt-mammalian target of rapamycin (mTOR) signaling pathway provides potent control over metabolic reprogramming during tumorigenesis by regulating nutrient uptake and allocating carbon and nitrogen to anabolic pathways to support *de novo* macromolecular synthesis (83). Akt activates a multitude of downstream effector molecules, with the serine/threonine kinase, mTOR, being a key regulator of protein synthesis, cell growth, and cellular metabolism. mTOR signaling increases aerobic glycolysis in cancer cells by increasing GLUT expression and stimulating glycolytic enzyme activity, including that of hexokinase and phosphofructose kinase (two essential enzymes of the glycolysis pathway) (50). mTOR is regulated by Akt-mediated inactivation of the mTOR upstream regulator tuberous sclerosis complex (TSC), where TSC functions by blocking the GTPase Rheb (Ras homology enriched in brain), freeing Rheb to directly activate mTOR complex 1 (mTORC1), which contains mTOR (84).

WNT controls mTOR signaling to affect cancer cell growth and tumor metabolism. In murine hyperplastic mammary tissue, WNT1 overexpression induces mTOR signaling. Regulation occurs at the level of GSK3β, which (in concert with AMPK), phosphorylates and directly activates TSC; thus, WNT-mediated GSK3β inhibition stimulates mTORC1 activity (85). Such β-catenin-independent WNT signaling via the mTOR pathway likely represents a conserved and general mechanism for noncanonical WNT regulation of glucose metabolism, as WNT3A-induced increases in aerobic glycolysis during osteoblast differentiation are dependent on mTORC activation yet independent of β-catenin (48). Likewise, in the context of prostate cancer cells, the WNT coreceptor LRP6 increases aerobic glycolysis in a

β-catenin-independent manner by directly activating Akt-mTORC1 signaling (86). Furthermore, my colleagues and I have found that WNT5A, signaling by the $Ca^{2+}$/WNT signaling pathway in melanoma cells, also increases aerobic glycolysis, mediated by the Akt-mTORC1 signaling module (13). Collectively, this work suggests that WNT/Akt-mTOR signaling is an important step in controlling cancer cell metabolism in a variety of tumor types. Although most of this evidence centers around β-catenin-independent mechanisms, Akt also promotes β-catenin signaling in cancer cells to increase aerobic glycolysis (87), suggesting that β-catenin signaling is downstream of Akt activity, presumably through Akt-mediated inhibition of GSK3β (88). Thus, the WNT signaling network also has the capacity to regulate cancer cell metabolism through cross talk with Akt-mTOR signaling.

## FUTURE PERSPECTIVE

This review demonstrates that there now exists an emergent body of evidence identifying the WNT signaling network as a regulator of cancer cell metabolism. Given that existing findings show that the canonical WNT pathway regulates changes in metabolic activities of cancer cells but is itself also regulated by the cellular metabolism machinery (including metabolic enzymes, by-products, nutrients, and nutrient-sensing pathways; Fig. 3) suggests that WNT/β-catenin signaling represents a critical node in the regulation of central metabolism in tumors. Hence, WNT signaling could provide cancer cells with metabolic flexibility, allowing them to respond to changes in the tumor microenvironment and alter their metabolic status accordingly.

Current research on this topic, however, is still in its infancy and much work is needed to determine the precise molecular mechanisms involved in the metabolic regulation of WNT signaling in differing tumor types. A lot of the molecular characterization to date has been done using cancer cell lines and xenograft models. While these offer convenient systems for identifying possible mechanisms of WNT-mediated metabolic regulation, such models are limited when studying cellular metabolism, not least in part because they do not recapitulate the tumor microenvironment, which provides nongenetic contributions to cancer cell metabolism through temporal gradients in pH, $O_2$, and nutrient availability within solid tumors (89, 90). Other cancer models, such as immunocompetent, genetically engineered mouse models of tumors (with the introduction of genetic alterations of the WNT pathways) or patient-derived tumor xenograft models that retain the same characteristics as the donor tumor, offer more sophisticated systems by which to study the role of WNT signaling in tumor metabolism. This will allow us to understand the complex molecular processes involved at a fundamental level.

Furthermore, the clinical implications of the findings highlighted in this article have yet to be understood. My colleagues and I have found that WNT5A signaling alters carbohydrate metabolism with directly opposite effects on breast cancer and melanoma cells, increasing OXPHOS in the former and aerobic glycolysis in the latter (13), which correlate with reduced and enhanced survival of patients, respectively. So, although most of the WNT signaling pathways studied to date result in enhanced aerobic glycolysis in cancer cells (Fig. 3), our work shows that this is clearly not always the case. As the net cellular response to WNT stimulation is ultimately determined by context-specific WNT network interactions (43, 44), our observation raises the intriguing possibility that distinct, context-dependent metabolic reprogramming of cancer cells by the WNT signaling network poses a direct effect on patient outcome. This represents a potentially hugely important direction for future investigations.

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