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# WISP1: Clinical Insights for a Proliferative and Restorative Member of the CCN Family

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## Abstract

As a proliferative and restorative entity, Wnt1 inducible signaling pathway protein 1 (WISP1) is emerging as a novel target for a number of therapeutic strategies that are relevant for disorders such as traumatic injury, neurodegeneration, musculoskeletal disorders, cardiovascular disease, pulmonary compromise, and control of tumor growth as well as distant metastases. WISP1, a target of the *wingless* pathway Wnt1, oversees cellular mechanisms that include apoptosis, autophagy, cellular migration, stem cell proliferation, angiogenesis, immune cell modulation, and tumorigenesis. The signal transduction pathways of WISP1 are broad and involve phosphoinositide 3-kinase (PI 3-K), protein kinase B (Akt), mitogen activated protein (MAP) kinase, c-Jun N-terminal kinase (JNK), caspases, forkhead transcription factors, sirtuins, c-myc, glycogen synthase kinase -3β (GSK-3β), β-catenin, miRNAs, and the mechanistic target of rapamaycin (mTOR). Ultimately, these signal transduction pathways of WISP1 can result in varied and sometimes unpredictable outcomes especially for cell survival, tissue repair, and tumorigenesis that demand increased insight into the critical role WISP1 holds for cellular biology and clinical medicine.

### Keywords

Akt; Alzheimer's; amyloid; apoptosis; autophagy; β-catenin; bone; cancer; cardiac; caspase; CCN4; erythropoietin; fibrosis; forkhead transcription factor; FoxO3a; liver; lung; metastases; miRNA; mTOR; PRAS40; pulmonary; sirtuin; SIRT1; stem cell; WISP1; Wnt

## DISCOVERY AND BACKGROUND OF WISP1

As a potential cellular protective entity, Wnt1 inducible signaling pathway protein 1 (WISP1) offers great promise for the development of novel therapeutic strategies against acute and chronic disorders throughout the body that may involve the nervous, musculoskeletal, cardiac, pulmonary, and vascular systems. However, as a proliferative agent, WISP1 can lead to complex biological outcomes and under some circumstances play a principal role during tumor formation. As a result, understanding the role of WISP1 in



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**CONFLICT OF INTEREST**

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multiple disorders becomes critical prior to being able to successfully target this pathway for clinical therapies.

*WISP1* was identified as a gene in a mouse mammary epithelial cell line [1] and subsequently determined to modulate gastric tumor growth [2]. The protein WISP1 is present in multiple sites throughout the body and is expressed in the epithelium, heart, kidney, lung, pancreas, placenta, ovaries, small intestine, spleen, and brain [3]. WISP1 is a matricellular protein that alters the signaling of other pathways to impact processes such as programmed cell death, extracellular matrix production, cellular migration, and mitosis [4]. WISP1 also can bind to leucine-rich proteoglycans that can impact the ability of other cells to anchor to the extracellular matrix [5].

As a member of the CCN family of proteins, WISP1 also is known as CCN4. The CCN family of proteins consists of six secreted extracellular matrix associated proteins and is defined by the first three members of the family that include Cysteine-rich protein 61, Connective tissue growth factor, and Nephroblastoma over-expressed gene [6]. Each family member contains four cysteine-rich modular domains that include insulin-like growth factor-binding domain, thrombospondin domain, von Willebrand factor type C module, and C-terminal cysteine knot-like domain. Overall, the CCN family has multiple cellular functions that include skeletal system development, vascular repair, cellular survival, and extracellular matrix growth.

WISP1 is a target of the *wingless* pathway Wnt1, a cysteine-rich glycosylated protein with signaling pathways that can modulate multiple processes that involve neuronal development, angiogenesis, immune cell modulation, tumorigenesis, and stem cell proliferation [7–16]. During injury paradigms, Wnt1 expression can be increased during spinal cord injury [17], ischemic brain injury [18], injury of vascular cells [19, 20], metabolic disturbance [19, 20], non-neuronal cell activation [21–26], and oxidative stress [15, 18, 24]. In addition, Wnt signaling in the brain also can be enhanced during physiological activity such as exercise [27] as well as play a role during mood disorders [28].

Wnt1 appears to be protective against toxic cellular environments. Several studies describe that loss of Wnt1 signaling can result in the cell death of osteoblast progenitors and differentiated osteoblasts [29], injury of human monocytes [8], increased ethanol-induced oxidative stress on bone formation [30], impaired bone repair [31], progressive spinal cord injury [16], loss of neurogenesis [32], enhanced cardiac aging [33], blockade of cellular proliferation [34], inhibition of wound healing with fibroblast to myofibroblast transition [35], increased nitrosative stress during diabetes [36], loss of stem cell differentiation [37], promotion of programmed cell death [3, 21, 38], and defective placental development [39]. In accordance with these studies, activation of Wnt1 or its down-stream signaling pathways can prevent cellular injury such as during experimental diabetes [19, 20, 40], ischemic stroke [18, 41], dopaminergic neuronal injury [7, 15, 23, 42], inflammatory cell loss during neurodegenerative disorders [21, 24, 26, 43], and neuronal synaptic dysfunction [44]. However, the protective and proliferative effects of Wnt1 can be detrimental especially in regards to the ability of Wnt1 signaling to assist with tumor progression. Wnt signaling activity can promote chemotherapy tumor resistance through noncoding RNAs [45] or

through enhanced angiogenesis [46] and may be a stimulus for numerous cancer disorders that include breast cancer [47], leukemia [48], and gastrointestinal inflammation and tumorigenesis [49].

## WISP1 SIGNALING

Initial work demonstrated that WISP1 can block p53 mediated DNA damage and prevent the induction of apoptosis [50]. However, WISP1 impacts multiple signal transduction pathways to affect cellular proliferation and cellular injury. WISP1 can modulate programmed cell death pathways such as autophagy [3, 51] and apoptosis [50, 52–54]. WISP1 can prevent apoptotic neuronal injury through mitochondrial pathways that minimize expression of the Bim/Bax complex while increasing the expression of $Bcl_{x(L)}$/Bax complex [55]. WISP1 also prevents phosphorylation of p38 mitogen activated protein (MAP) kinase and c-Jun N-terminal kinase (JNK) [52] and blocks c-Myc mediated apoptosis [54]. Ultimately, WISP1 can inhibit caspase activation [52, 53, 55].

WISP1 is intimately involved with other pathways that can drive cellular proliferation and survival. These include cellular protective pathways of phosphoinositide 3 –kinase (PI 3-K) and protein kinase B (Akt) [56–63] as well as forkhead transcription factors, sirtuins, and the mechanistic target of rapamaycin (mTOR). For example, activation of Akt limits cell injury and prevents the detrimental effects of amyloid (Aβ) toxicity [21, 64, 65] and oxidative stress [66–69]. PI 3-K and Akt also are critical for agents such as growth factors to promote cell survival. The growth factor and cytokine erythropoietin (EPO) activates Akt through its phosphorylation of $serine^{473}$ [70, 71] and prevents vascular cell demise through silent mating type information regulator 2 homolog 1 (SIRT1) cell longevity pathways [72]. EPO utilizes Akt to block cell injury during Aβ exposure [26], promote the survival of retinal ganglion cells during N-methyl-d-aspartate (NMDA) toxicity [73], enhance the myocardial protective function of mobilized peripheral blood mononuclear cells [74], foster anti-inflammatory effects [75], protect against sepsis [76], limit renal cell injury [77], and limit cellular injury during models of oxidative stress [78–81]. Similar to EPO, other trophic factors also rely upon the PI 3-K and Akt pathways to foster cellular survival during toxic environments such as insulin-like growth factor-1 (IGF-1) [56], insulin [82], and brain derived neurotrophic factor [83].

Mammalian forkhead transcription factors of the O class [FoxO1, FoxO3, FoxO4, and FoxO6) have multiple cellular functions that involve cell growth, cell-cycle regulation, tumorigenesis, metabolism, and cell survival [19, 24, 84–92]. Akt can block apoptosis by phosphorylating FoxO proteins, promoting the sequestration of FoxO proteins by 14-3-3 in the cytoplasm, and ultimately blocking their transcription [53, 78, 93]. Once forkhead transcription factor activity is inhibited, Aβ toxicity can be limited [92, 94], vascular survival is enhanced during experimental diabetes [95, 96], erythroid progenitors differentiation is promoted [97], smooth muscle proliferation is enhanced [98], and the detrimental effects of neonatal hypoxia-ischemic encephalopathy may be reduced [99]. However, it is important to note that forkhead transcription factor blockade also may be detrimental during unchecked tumor growth such as in gastric cancer [100] and lymphoma [101].

Sirtuins are the mammalian homologues of Sir2 and are class III histone deacetylases. These histone deacetylases are nicotinamide adenine dinucleotide [NAD+) dependent and transfer acetyl groups from ε-N-acetyl lysine amino acids that exist on the histones of DNA to regulate transcription. Although histone deacetylases primarily oversee DNA transcription, they also can affect post-translational changes of proteins such as the ability of the sirtuin SIRT1 to control the post-translational phosphorylation of forkhead transcription factors [95, 96]. Of the seven mammalian homologues of Sir2 that include SIRT1 through SIRT7, SIRT1 plays a significant role in oxidative stress, cell metabolism, genomic stability, cell survival, neurodegenerative disease, infection, and cardiovascular disease [102–107]. In regards to cytoprotection, SIRT1 activation can prevent hypoxic injury in retinal ganglion cells [108], modulate cell longevity [109, 110], protect against high-fat diet-induced metabolic abnormalities [111, 112], increase cellular survival during anoxia and ischemia [113, 114], reduce Aβ toxicity [115], reverse impaired fat and glucose metabolism [12, 116–118], maintain mitochondrial processing and quality through autophagy [119], foster cellular protection against radiation [120], protect against renal cell aging [121], block apoptotic pathways in preadipocytes [122], and modulate forkhead mediated apoptotic pathways [53, 72, 96, 118, 123–126]. Yet, other studies suggest that to achieve cytoprotection through sirtuin pathways, the level of sirtuin activity may be critical [53, 72, 115, 127], since SIRT1 gene polymorphisms may affect protein expression during cardiovascular disease [105], SIRT1 activity can promote tumor growth [128, 129], and reduction in SIRT1 activity has been reported to enhance the cytoprotective effects of IGF-1 [130].

mTOR, also known as the mammalian target of rapamycin and FK506-binding protein 12-rapamycin complex-associated protein 1, is a 289-kDa serine/threonine protein kinase that oversees multiple functions that include gene transcription, protein formation, cellular metabolism, cytoskeleton components, tumor growth, and cellular survival [131–135]. mTOR is a critical component of the protein complexes mTOR Complex 1 [mTORC1) and mTOR Complex 2 [mTORC2) [136, 137]. Rapamycin, a macrolide antibiotic from Streptomyces hygroscopicus, inhibits the target of rapamycin [TOR) activity in yeast. In mammals, mTORC1 is more sensitive to the inhibitory effects of rapamycin than mTORC2 [138]. mTORC1 is composed of Raptor (Regulatory-Associated Protein of mTOR), the proline rich Akt substrate 40 kDa (PRAS40), Deptor (DEP domain-containing mTOR interacting protein), and mLST8/GbL (mammalian lethal with Sec13 protein 8, termed mLST8). mTORC2 also includes mLST8 and Deptor, but has additional components that are Rictor (Rapamycin-Insensitive Companion of mTOR), the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) [136, 137]. Similar to WISP1, mTOR signaling is associated with PI 3-K, Akt, forkhead transcription factors, PRAS40, AMP activated protein kinase (AMPK), and p70 ribosomal S6 kinase (p70S6K) to affect cellular survival through programmed cell death pathways that involve apoptosis, autophagy, and necroptosis [60, 62, 63, 76, 79, 139–149]. For example, Akt can control mTORC1 activity through the modulation of hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex, an inhibitor of mTORC1 [150–152]. Akt can phosphorylate TSC2 on multiple sites that leads to the destabilization of TSC2 and disruption of its interaction with TSC1. Control of the TSC1/TSC2 complex principally occurs though the phosphorylation of TSC2 by Akt, extracellular

signal-regulated kinases (ERKs), activating protein p90 ribosomal S6 kinase 1 (RSK1), AMPK, and glycogen synthase kinase -3β (GSK-3β). In regards to programmed cell death with mTOR signaling, these pathways do not always function independently and can influence one another. Therapies that target mTORC1 and mTORC2 to overcome leukemic cell resistance may require the induction of apoptosis with the repression of autophagy [3, 153]. In addition, WISP1 can prevent cell death primarily through inhibition of GSK-3β and apoptotic pathways with additional pathways that require inhibition of autophagy [51]. Inhibition of mTOR in acute lymphoblastic leukemia leads to autophagy dependent cell loss with features that are consistent with necroptosis [154].

WISP1 can block cellular injury through the PI 3-K and Akt pathways. Activation of Akt in association with WISP1 occurs during DNA damage [50], mechanical strain in osteoblasts [155], fibroblast proliferation in airway remodeling [156], cardiomyocyte injury [52], vascular smooth muscle proliferation [157], oxidative stress [51, 53, 55], and Aβ exposure [152]. Following Akt activation, WISP1 results in the inhibitory phosphorylation of GSK-3β [51, 52, 55, 156]. During the inhibition of GSK-3β, β-catenin is not phosphorylated, ubiquinated, or degraded which allows translocation of this “anti-apoptotic” protein to the nucleus [8, 10, 15, 21, 27, 158, 159]. As a result, WISP1 during GSK-3β inhibition maintains the integrity of β-catenin and promotes the translocation of β-catenin to the nucleus in neurons [51], cardiomyocytes [52], hepatocytes [160], epithelial lung cells [161], and growth plate cartilage [31] that can lead to tissue repair. Interestingly, β-catenin that also is dependent upon Wnt signaling promotes the expression of WISP1 [162, 163]. However, it should be noted that WISP1 maintenance of β-catenin also can lead to tumor progression [164], metastatic disease [165], and represent a poor clinical prognosis during cancer diagnosis [166].

As previously described, the Wnt signaling pathway can protect cells during a number of injury paradigms. In such cases, cytoprotection may be afforded through forkhead transcription post-translational phosphorylation and inhibition. During oxidative stress, osteoblastic differentiation is preserved through up-regulation of Wnt signaling and inhibition of FoxO3a activity [167]. In hepatic cells that are exposed to chronic oxidative injury, Wnt signaling blocks FoxO3a activity to prevent apoptotic cell death [168]. Furthermore, trophic factors such as EPO have been shown to use a Wnt1 dependent mechanism to phosphorylate FoxO3a and block the trafficking of FoxO3a to the cell nucleus to prevent apoptotic demise [19]. Wnt signaling also affords protection of inflammatory microglial cells through forkhead transcription factor inhibition [24]. Through similar pathways, WISP1 protects neurons through the posttranslational phosphorylation of FoxO3a, by sequestering FoxO3a in the cytoplasm with protein 14-3-3, and by limiting deacytelation of FoxO3a [53].

Sirtuins, such as SIRT1, are effective mediators of cell survival during toxic insults if these histone deacetylases remain intact during cellular insults. Loss of sirtuin activity can be a result of the nuclear degradation of the sirtuin SIRT1 [127] and lead to the subsequent activation of caspases [108, 127]. SIRT1 degradation may be mediated by apoptotic pathways linked to p38 [169] and JNK1 [170]. WISP1 cytoprotection appears to be dependent upon SIRT1 pathways. WISP1 maintains SIRT1 expression and increases SIRT1

activity during oxidative stress to afford cellular protection [53]. In addition, WISP1 also fosters SIRT1 nuclear translocation [53] that is usually necessary for protection against apoptotic injury [72, 96, 171]. WISP1 relies upon the modulation of FoxO3a and caspase activity during oxidative stress to maintain the integrity of SIRT1 [53] similar to other injury paradigms [123, 126, 172]. Over-expression of FoxO3a leads to increased caspase 1 and caspase 3 activity during oxidant stress [95, 173]. WISP1 blocks FoxO3a activity through the inhibitory post-translational phosphorylation of FoxO3a and prevents caspase 1 and caspase 3 activation during oxidative stress that would otherwise lead to the degradation of SIRT1.

Wnt signaling that includes WISP1 employs several components of the mTOR pathway that can oversee cellular survival and proliferation [174, 175]. In injury models that involve cultured macrophages or neurons exposed to hypoxia, Wnt1 expression is increased [18, 176]. Enhancement of Wnt signaling results in increased Akt activity that promotes cellular protection [18, 21] and also leads to elevated mTOR activity to foster human β-cell proliferation [177] and epithelial stem cell growth [178]. Without mTOR activation, Wnt1 has been shown to lose the ability to support cellular proliferation [179]. The growth factor EPO requires Wnt1, mTOR, and p70S6K to foster cytoprotection for microglial cells during oxidant stress [25] and during Aβ toxicity [26].

In regards to WISP1 and mTOR, WISP1 targets several pathways of mTOR by activating mTOR and phosphorylating p70S6K and 4EBP1 through the control of the regulatory mTOR component PRAS40 [180]. WISP1 controls PRAS40 by sequestering this protein in the intracellular compartment. WISP1 also drives the post-translational phosphorylation of AMPK by differentially decreasing phosphorylation of TSC2 at $Ser^{1387}$, a target of AMPK, and increasing phosphorylation of TSC2 at $Thr^{1462}$, a target of Akt1 [152]. WISP1 increases TSC2 activation by limiting AMPK activation. When active, AMPK can phosphorylate TSC2 on $serine^{1387}$ to ultimately inhibit the activity of mTOR and the mTORC1 complex [181]. The ability of WISP1 to limit TSC2 ($Ser^{1387}$) phosphorylation appears to allow WISP1 to increase the activity of downstream mTOR components, such as p70S6K. During Aβ exposure, WISP1 can phosphorylate mTOR, p70S6K and the eukaryotic initiation factor 4E-binding protein 1 (4EBP1) [180] which is indicative of increased mTOR activity [182]. However, during gene silencing of TSC2, phosphorylation of p70S6K is further enhanced during Aβ exposure alone and in the presence of WISP1, suggesting that down-regulation of phosphorylation of the TSC2 ($Ser^{1387}$) by WISP1 contributes to enhanced activity of the mTOR pathway [152]. On the other end, WISP1 also increases TSC2 activity by promoting the Akt pathway through phosphorylation of TSC2 at $Thr^{1462}$. However, it appears that a minimal level of TSC2 activity is necessary to modulate WISP1 cytoprotection, since gene knockdown of TSC2 impairs the ability of WISP1 to provide cytoprotection [152].

## WISP1: A PROLIFERATIVE AND REPARATIVE AGENT

Increasing focus upon WISP1 and its cellular pathways has fueled enthusiasm for new therapeutic strategies for this CCN family member. In models of third degree burns in mouse models, WISP1 mRNA transcripts are up-regulated during wound healing, suggesting that WISP1 may be a key element for tissue repair [183]. Bone formation

following growth plate cartilage injury also has been shown to involve expression of the *WISP1* gene [31]. During mechanical stretch injury of lung epithelial cell injury, WISP1 is up-regulated in stretched cells and loss of WISP1 prevents mesenchymal transition necessary for the repair of lung epithelial cells [184]. WISP1 through β-catenin/p300 may be necessary for epithelial cell repair during inflammatory lung injury [161]. WISP1 also promotes mesenchymal cell proliferation and osteoblastic differentiation with the repression of chondrocytic differentiation to further bone development [185] and fracture repair [186]. WISP1 may enhance osteogenesis through bone morphogenetic protein 2 (BMP-2) [187]. Bone formation through parathyroid hormone treatment also may proceed through increased WISP1 expression [188]. However, in some cases, WISP1 may be considered a factor for the progression of osteoarthritis since WISP1 can result in chondrocyte hypertrophy through transforming growth factor-β signaling and activin-like kinase (ALK)5 [189].

In the nervous system, WISP1 may have a vital role in blocking cell death and promoting tissue repair. During oxidant stress with oxygen-glucose deprivation, WISP1 expression is up-regulated and WISP1 is necessary to confer neuronal protection by limiting the expression of the Bim/Bax complex, increasing the expression of $Bcl_{x[L]}$/Bax complex, and blocking cytochrome c release and caspase 3 activation [55]. WISP1 autoregulates its own expression that is dependent upon increased β-catenin activity [51, 190]. WISP1 prevents the phosphorylation and degradation of β-catenin to maintain the activity of β-catenin. This promotion of β-catenin activity also serves to limit the induction of autophagy [51]. Through an autoregulatory loop, WISP1 also has been shown to enhance neuronal survival by limiting FoxO3a deacytelation, blocking caspase 1 and 3 activation, and fostering SIRT1 nuclear trafficking [53]. In regards to immune mediated therapies that may be effective against neurodegenerative disorders such as Alzheimer's disease [133, 191–196], WISP1 can protect central nervous system microglial cells against Aβ toxicity by employing mTOR downstream pathways that modulate PRAS40 [180] and TSC2 [152] to increase mTOR activity [197].

WISP1 also may be a significant factor for vascular and cardiovascular repair. Following saphenous vein crush injury, WISP1 expression is selectively up-regulated and may support vascular repair and regeneration [198]. WISP1 also promotes vascular smooth muscle proliferation that may be important for tissue repair during injury or affect restenosis following vascular grafting [157, 199]. Yet, WISP1 does not appear to lead to cellular proliferation in aging vascular cells [200] and may promote senescence [201]. WISP1 has been shown to be effective in rescuing cardiomyocytes from doxorubicin toxicity, a chemotherapeutic agent that leads to acute and chronic cardiac and renal injury [202]. Through PI3-K, Akt, and survivin, WISP1 prevents cardiomyocyte cell death [52].

The reparative properties of WISP1 may be the result of the ability of WISP1 to influence stem cell proliferation, migration, and differentiation. WISP1 is up-regulated during stem cell migration [183] and WISP1 may be one of several components that affect induced pluripotent stem cell reprogramming [203, 204]. WISP1 is differentially regulated during human embryonic stem cell and adipose-derived stem cell differentiation. For example, WISP1 is up-regulated in human embryonic stem cells and repressed in adipose-derived

stem cells during hepatic differentiation [205]. WISP1 in conjunction with β-catenin also may be necessary for the differentiation of marrow derived mesenchymal stem cells [206].

Although the proliferative nature of WISP1 may play a vital role during cell recovery and tissue repair, evidence also exists for CCN family members [207] and WISP1 to lead to fibrotic tissue injury such as during cardiac remodeling following infarction [208]. WISP1 expression also is significantly elevated in primary fibroblasts during idiopathic pulmonary fibrosis [209] with WISP1 expression potentially regulated by the microRNA [miRNA) miR-92a [210]. WISP1 expression has been correlated with fibrosis in models of liver fibrogenesis [211], asthma airway remodeling [156], and in murine models of alveolar epithelial cell hyperplasia [212].

## THE VARIABLE IMPACT OF WISP1 IN TUMORIGENESIS

WISP1 may play a role in tumor cell development and progression. Early studies identified that the genomic DNA of WISP1 was amplified in colon cancer cell lines as well as in human colon tumors [1]. Subsequent work has suggested an association of WISP1 with chronic inflammatory bowel disease such as ulcerative colitis [162]. The increased expression of Wnt1, WISP1, survivin, and cyclin-D1 observed in colorectal cancer may be suggestive that these pathways work synergistically to promote cell cycle progression and tumor growth while blocking apoptosis [213]. WISP1 expression may be suggestive of more advanced progression in some tumors, such as those associated with breast cancer [214, 215] and esophageal squamous cell carcinoma [216]. During chronic ethanol consumption, WISP1 has been implicated in hepatic cell proliferation that can result in liver cancer [160]. WISP1 has been associated with abnormal expression and gene fusion during lung adenocarcinoma [217]. In the nervous system, WISP1 expression is increased in neurofibromatosis type 1 tumorigenesis [218].

Although variants of WISP1 have been described to be extremely aggressive in promoting cell growth in scirrhous gastric carcinomas [219] and cholangiocarcinoma [220] leading to striking cellular transformation and rapid piling-up growth, non-variant WISP1 expression in lung cancer cells has been shown to be significantly less invasive, may inhibit lung metastases, and may block tumor cell invasion and motility [221]. Differential expression of CCN family members in breast cancer also has suggested that WISP1 may function to limit breast cancer growth [222]. Furthermore, Notch1 activation that results in increased WISP1 expression can suppress melanoma growth [223]. Suppression of melanoma tumor growth is lost during WISP1 gene knockdown [223]. However, this ability of WISP1 to limit metastatic disease may be tissue specific since WISP1 expression and activity in experimental models may promote early prostate cancer and foster distant bone metastatic disease [224].

## FUTURE PROSPECTIVES AND CONSIDERATIONS

As both a proliferative and restorative entity, WISP1 holds promise for a number of emerging therapeutic strategies that can address traumatic injury, neurodegeneration, musculoskeletal disorders, cardiopulmonary and vascular disease, and the control of tumor growth as well as distant metastases (Fig. 1). WISP1 is a target of the *wingless* pathway

Wnt1 that is closely tied to pathways of neuronal and vascular development, cytoprotection, inflammatory modulation, and cancer cell growth. WISP1 is linked to multiple signal transduction pathways that include PI 3-K, Akt, MAP kinases, JNK, caspases, forkhead transcription factors, sirtuins, c-myc, GSK-3β, β-catenin, miRNAs, and mTOR. Through these pathways, WISP1 signaling can ultimately alter the course of programmed cell death pathways such as apoptosis and autophagy to promote cytoprotection and tissue repair.

However, WISP1 has a complex relationship with several cellular pathways that can lead to variable biological and clinical outcomes. For example, trophic factors such as insulin-like growth factor-1 (IGF-1) [56], insulin [82], brain derived neurotrophic factor [83], and EPO [70, 73, 75–77, 225–228] rely upon Akt activation to protect cells against toxic cellular insults. In particular, EPO activates Akt using Wnt signaling pathways to phosphorylate FoxO proteins, promote the sequestration of these proteins by 14-3-3 in the cytoplasm, and block the transcription of FoxO proteins [19, 72, 78, 97, 229]. WISP1 also affords cytoprotection through the post-translational phosphorylation and inhibition of FoxO3a [53]. Under some conditions, blockade of these signal transduction pathways may be detrimental since inhibition of FoxO proteins can promote unwanted tumor growth such as in gastric cancer [100], lymphoma [101], and hepatic cancer [230]. Furthermore, agents such as EPO that are used for the treatment of anemia can be contraindicated in patients with hypertension, since both acute and long-term administration of EPO can significantly elevate mean arterial pressure [231]. These observations may be tied to Wnt signaling and WISP1. Polymorphisms of WISP1 have been associated with hypertension in Japanese men related to both systolic and diastolic pressure [232].

Similar caveats hold true for WISP1 with SIRT1 and mTOR. WISP1 maintains SIRT1 expression and increases SIRT1 activity during oxidative stress to foster cellular protection [53]. Yet, enhanced SIRT1 activity may lead to tumor growth [128, 129]. In addition, some protective mechanisms appear to require a limited activation of SIRT1 [53, 72, 115, 127] and others may necessitate an actual reduction in SIRT1 activity, such as those with IGF-1 [130]. In consideration of mTOR, WISP1 requires activation of mTOR signaling with inhibition of specific pathways such as PRAS40 to offer cellular protection against Aβ exposure [152, 180]. Although these studies suggest a role for WISP1 in disorders such as Alzheimer's disease through the activation of mTOR pathways, one must proceed with caution since the degree of mTOR activation may be critical in treating neurodegenerative disorders [133, 137]. In favor of mTOR activation, mTOR activation has been shown to protect neuronal networks controlling memory [233]. Activity of mTOR also may be required for long-term memory formation [234], the reconsolidation phase of traumatic memory [235], and memory restoration during vascular dementia [236]. Loss of mTOR activity can impair long-term potentiation and synaptic plasticity in animal models of Alzheimer's disease [237]. Increased mTORC1 activity may necessary to regulate the β-site amyloid precursor protein (APP)-cleaving enzyme 1 (β-secretase, BACE1) that promotes Aβ accumulation in Alzheimer's disease, since high mTORC1 activity depletes BACE1 and is able to reduce Aβ generation [238]. Yet, other work suggests that that inhibition of mTOR may be necessary for the treatment of epilepsy [137, 239, 240], some stages of Alzheimer's disease [133, 137, 241, 242], and drug addiction associated memories [243]. In studies with Alzheimer's disease, blockade of mTOR can lead to a reduction in BACE1 to reduce Aβ

accumulation [149], enhance Aβ clearance in cell lines and animal models, and improve spatial learning through the induction of autophagy [244].

In addition to the nervous system, WISP1 is a novel target for new drug development for disorders such as wound healing, bone repair, loss of bone density with aging, and pulmonary disease. Targeting WISP1 also may be critical for repair of vascular trauma as well as preventing stenosis of vessels following grafting [157, 199]. WISP1 may be effective as a co-treatment to prevent cardiomyocyte injury during chemotherapy regimens that lead to cardiotoxicity [52]. Yet, developing WISP1 for such disorders must be carefully focused since increased WISP1 expression may have clinical side effects such as fibrotic tissue injury that result in liver fibrogenesis [211], asthma airway remodeling [156], and alveolar epithelial cell hyperplasia [212].

As a proliferative agent, WISP1 also can impact tumor cell growth by increasing the risk for disorders that can lead to tumorigenesis [162] and also directly resulting in several types of cancer such as colon cancer [1], breast cancer [214, 215], neurofibromatosis type 1 tumorigenesis [218], lung adenocarcinoma [217], and esophageal squamous cell carcinoma [216]. However, the relationship of WISP1 to tumor cell development and progression requires further investigation. Although variants of WISP1 can lead to aggressive tumor cell growth [219], non-variant WISP1 expression can be less invasive and may inhibit metastases by blocking tumor cell invasion and motility [221]. In addition, other studies provide additional support for WISP1 to act as an “anti-tumor” agent in breast cancer [222] and melanoma [223]. The mechanisms that determine the ability of WISP1 to affect cell cycle pathways as well as programmed cell death may be one consideration to provide further insight into the necessary signal transduction pathways of WISP1 for developing clinically effective cancer treatments.

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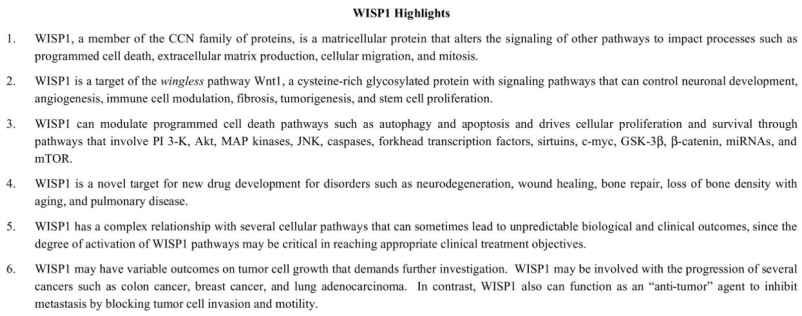


**Fig. 1.**

Topical Highlights for the Restorative and Proliferative Effects of WISP1.