



Published in final edited form as:  
*J Transl Sci.* 2016 ; 1(3): 83–85.

## Picking a bone with WISP1 (CCN4): new strategies against degenerative joint disease

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### Abstract

As the world's population continues to age, it is estimated that degenerative joint disease disorders such as osteoarthritis will impact at least 130 million individuals throughout the globe by the year 2050. Advanced age, obesity, genetics, gender, bone density, trauma, and a poor level of physical activity can lead to the onset and progression of osteoarthritis. However, factors that lead to degenerative joint disease and involve gender, genetics, epigenetic mechanisms, and advanced age are not within the control of an individual. Furthermore, current therapies including pain management, improved nutrition, and regular programs for exercise do not lead to the resolution of osteoarthritis. As a result, new avenues for targeting the treatment of osteoarthritis are desperately needed. Wnt1 inducible signaling pathway protein 1 (WISP1), a matricellular protein and a downstream target of the wingless pathway Wnt1, is one such target to consider that governs cellular protection, stem cell proliferation, and tissue regeneration in a number of disorders including bone degeneration. However, increased WISP1 expression also has been associated with the progression of osteoarthritis. WISP1 has an intricate relationship with a number of proliferative and protective pathways that include phosphoinositide 3-kinase (PI 3-K), protein kinase B (Akt), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), interleukin -6 (IL-6), transforming growth factor- $\beta$ , matrix metalloproteinase, small non-coding ribonucleic acids (RNAs), sirtuin silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), and the mechanistic target of rapamycin (mTOR). Taken together, this complex association WISP1 holds with these signaling pathways necessitates a fine biological regulation of WISP1 activity that can offset the progression of degenerative joint disease, but not limit the cellular protective capabilities of the WISP1 pathway.

### Keywords

Akt; apoptosis; arthritis; autophagy; degenerative joint disease; IL-6; microRNA; mTOR; *NF- $\kappa$ B*; osteoarthritis; PI 3-K; SIRT1; stem cells; WISP1; Wnt signaling

### The fine targeting of WISP1 for degenerative joint disease

Osteoarthritis is a chronic disorder that results from cartilage degeneration and mechanical stress imposed upon the skeletal system. Low bone mass and structural deterioration of bone

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tissue eventually lead to bone fragility and increased susceptibility to fractures. As a result, individuals with this disorder have impaired mobility and pain that can occur in hip joints, the shoulder, spine, knees, feet, and hands. The most severe fracture that can result from osteoarthritis involves the hip that requires hospitalization and leads to permanent disability in 50% of individuals and fatality in another 20% of individuals.

In developed nations, osteoarthritis is considered to be one of the ten most common disabilities in aged individuals especially those that remain active in the workforce [1]. According to the World Health Organization [2], at least 15% of all adults over the age of 60 are believed to suffer from this disorder with women having greater prevalence of osteoarthritis than men. It is estimated that worldwide 9.6% of men and 18.0% of women over the age of 60 suffer with osteoarthritis. With advancing age of the world's population, the incidence of osteoarthritis is expected to increase. By the year 2050, at least 130 million people throughout the world may suffer from osteoarthritis.

Risk factors that can lead to the progression of osteoarthritis involve advanced age, obesity, genetics, gender, bone density, trauma, and a poor level of physical activity [3]. Preventive measures can be instituted to decrease the onset of osteoarthritis such as protective clothing and gait aides to avoid trauma, regular programs for exercise, and nutritional programs that address proper weight management. Yet, factors such as gender, genetics, and advanced age are beyond an individual's control and therapies directed at pain management offer symptomatic relief at best. Furthermore, complex epigenetic mechanisms that oversee DNA methylation, small non-coding RNAs (microRNAs), post-translation protein modification, and histone deacetylation may present additional risk factors for the development of osteoarthritis.

One exciting therapeutic target for osteoarthritis that is emerging as a novel consideration is Wnt1 inducible signaling pathway protein 1 (WISP1), also known as CCN4 [4-6]. WISP1 is a matricellular protein and a downstream target of the *wingless* pathway Wnt1 [7]. In addition, WISP1 is a member of the CCN family of proteins. The CCN family of proteins contains six secreted extracellular matrix associated proteins. They are defined by the first three members of the family that include Cysteine-rich protein 61, Connective tissue growth factor, and Nephroblastoma over-expressed gene [8,9]. WISP1 is expressed in the brain, heart, kidney, lung, pancreas, placenta, epithelium, ovaries, small intestine, and spleen [9]. Of interest, WISP1 can govern cellular survival, metabolism, and stem cell proliferation and maintenance [10] and can modulate epigenetic pathways [9-11].

WISP1 may be important for tissue repair and regeneration during a number of diseases. For example, WISP1 can control induced pluripotent stem cell reprogramming [12,13] and is one of several genes that are over-expressed during pancreatic regeneration [14]. WISP1 also can foster vascular regeneration during saphenous vein crush injury [15]. WISP1 expression is increased during stem cell migration [16] and is repressed during hepatic differentiation in adipose-derived stem cells [17]. WISP1 leads to vascular smooth muscle proliferation that can assist with tissue repair during injury [18,19]. WISP1 also is tightly linked to metabolic homeostasis [14] and appears to have a modulatory role in cell senescence. WISP1 can control cellular senescence [20] to a degree that does not promote

excessive cellular proliferation in aging vascular cells [21] that could lead to atherosclerosis during diabetes mellitus.

In regards to the musculoskeletal system, WISP1 has been shown to promote mesenchymal cell proliferation and osteoblastic differentiation with the repression of chondrocytic differentiation to further bone development [22] and assist with fracture repair [23]. Bone formation after growth plate cartilage injury involves expression of the *WISP1* gene [24]. WISP1 may increase osteogenesis activity through bone morphogenetic protein 2 [25] and be required for bone formation through parathyroid hormone treatment [26]. WISP1 also oversees bone morphogenetic protein-3 stimulated mesenchymal stem cell proliferation [27].

Given the ability of WISP1 to control cellular proliferation in the musculoskeletal system, WISP1 and related members of the CCN family have emerged as potential targets for disorders such as osteoarthritis and rheumatoid arthritis. CCN1, CCN2, CCN4, and CCN5 have been found to be expressed to a greater extent in knee cartilage during osteoarthritis and rheumatoid arthritis when compared to normal controls [28]. In particular, WISP1 is considered a significant factor for the progression of osteoarthritis. In osteoarthritis synovial fibroblasts, WISP1 can activate  $\alpha\beta 5$  integrin, phosphoinositide 3-kinase (PI 3-K), protein kinase B (Akt), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) pathways that result in the up-regulation of interleukin -6 (IL-6) production [29]. WISP1 leads to chondrocyte hypertrophy through transforming growth factor- $\beta$  (TGF- $\beta$ ) signaling and activin-like kinase (ALK)1/Smad 1/5/8 pathway [30]. In models of osteoarthritis, WISP1 controls chondrocyte and macrophage matrix metalloproteinase and aggrecanase expression that results in articular cartilage damage [31]. Furthermore, overexpression of WISP1 can lead to increased cartilage damage while blocking of the upstream canonical Wnt signaling pathway can limit cartilage damage [32]. Interestingly, the detrimental effects of WISP1 in arthritic disease somewhat parallel the ability of WISP1 to also promote fibrotic tissue injury. WISP1 expression has been tied to idiopathic pulmonary fibrosis possibly regulated by the microRNA miR-92a [33] and linked to fibrosis in models of liver fibrogenesis [34].

In light of the emerging knowledge of WISP1 signaling pathways, promoting the down-regulation of WISP1 expression in arthritic joint disease appears to open new therapeutic strategies for this disabling disorder. Yet, WISP1 also is associated with a number of cellular pathways that are supportive of bone development and repair and protective against cell injury that include silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) SIRT1 [35] and mechanistic target of rapamycin (mTOR) (36). WISP1 can protect cells against oxidative stress [35,37], control pathways of apoptosis and autophagy [36,38], and prevent inflammatory cell injury during exposure to toxins such as  $\beta$ -amyloid [39,40]. Therefore, a careful targeted approach that limits WISP1 activity but does not negatively impact cellular protective pathways may be required for the development of WISP1 as a novel treatment for musculoskeletal disorders.

## Acknowledgments

This research was supported by the following grants to Kenneth Maiese: American Diabetes Association, American Heart Association, NIH NIEHS, NIH NIA, NIH NINDS, and NIH ARRA.

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