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BITS AND BYTES

Will o' the wisp: CCN4 as a novel molecular target in osteoarthritis

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Abstract Osteoarthritis (OA), or degenerative arthritis, is characterized by mechanical stress-induced changes in cartilage and bone. OA is a leading cause of chronic disability in North America and Europe. A recent study written by Blom and colleagues (Arthritis and Rheumatism 2009; 60:501–12) showed that elevated wnt signaling was observed in experimental OA as well as in patient samples. The authors found that the known wnt target WISP-1 (CCN4) was also overexpressed; CCN4 was sufficient to recapitulate an OA phenotype in vitro and in vivo, suggesting that CCN4 may be a novel target for drug intervention in OA. This commentary summarizes these exciting findings.

Keywords Osteoarthritis · CCN4 · WISP-1 · Wnt · Cartilage

The years 2000–2010 were declared the Bone and Joint Decade. This global initiative was intended to improve the lives of people with musculoskeletal disorders, and to advance understanding and treatment of musculoskeletal disorders through prevention, education and research. Musculoskeletal disorders, the most common causes of severe long-term pain and physical disability, affect hundreds of millions of people across the world. Musculoskeletal disorders include arthritis which is inflammation of one or more joints, which results in pain, swelling, stiffness, and limited movement. Osteoarthritis (OA), the most common arthritic disease in the world and the leading cause of disability in the United States especially among the elderly, affects at least 27 million persons afflicted with OA in the United States, costing the economy approximately $60 billion annually (Elders 2000; Lawrence et al. 2008). By 2020, the overall cost of OA is anticipated to amount to nearly $100 billion dollars including increased spending on diagnosis andtherapy, side-effect prevention and lost earnings (Oliviero et al. 2010). In total, it is estimated that approximately 40% of adults aged over 70 suffer from OA of the knee, with the vast majority of these suffering from limitation in movement and a significant subset showing impaired ability to conduct their daily business (Oliviero et al. 2010).

The principal method of treating OA is to address pain through taking nonsteroidal anti-inflammatory drugs (NSAIDs) (Altman and Barkin 2009). The limited function observed with OA can be improved with a wide variety of rehabilitative interventions including joint specific exercises, improved physical fitness and weight loss. However, if ultimately the entire joint becomes severely degenerated, surgical treatment is required (Lützner et al. 2009).

The molecular basis of OA involves cartilage erosion and synovial inflammation, including the presence of cytokines such as tumor necrosis factor-α and interleukin-1-β and matrix degrading metalloproteinases (MMPs) (Burrage and Brinckerhoff 2007). Characterizing the pathophysiological events responsible for OA is therefore essential to identifying appropriate targets for drug therapy in OA.

Recently, evidence has been provided that the wnt family of proteins may plays a key role in OA (Blom et al. 2010). Members of the wnt/frizzled pathway have been shown to be upregulated in cells of OA patients (Ijiri et al. 2002; Nakamura et al. 2005). The CCN family of matricellular proteins are known wnt targets; three of these (CCN4-6) were initially identified based on the fact they were wnt-inducible secreted proteins (Pennica et al. 1998; Si et al. 2006; Chen et al. 2007; Chen and Leask 2009; Lemaire et al. 2010). Of the CCN family members, especially strong

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evidence links CCN4 (WISP-1) to bone remodeling. For example, CCN4 promotes BMP-2-mediated osteoblast differentiation, is induced during fracture repair and promotes mesenchymal cell proliferation and osteoblastic differentiation while repressing chondrocytic differentiation (French et al. 2004). CCN4 appears to act by stimulating Smad 1/5/8 phosphorylation and activation via integrin alpha5beta1 (Ono et al. 2010), a known receptor for the CCN proteins (Lin et al. 2003; Chen et al. 2004; Hoshijima et al. 2006; Gao and Brigstock 2006).

A recent study (Blom et al. 2009) showed that Wnt-16 and Wnt-2B and their target CCN4/WISP-1 was strongly increased in the synovium and cartilage of mice with experimental OA. Increased CCN4 expression was also found in human OA cartilage and synovium. Significantly, recombinant CCN4 was able to elicit the release of MMPs and aggrecanase from macrophages and chondrocytes, in a fashion that did not rely in interleukin-1. Moreover, when CCN4 was delivered to mouse joints using an adenovirus, elevated MMP and aggrecanase expression resulted, and cartilage damage was observed.

These data indicate that CCN4 may be sufficient to cause OA in humans, and that CCN4 may in the future prove to be an appropriate target for drug intervention in OA.

References

Altman R, Barkin RL (2009) Topical therapy for osteoarthritis: clinical and pharmacologic perspectives. Postgrad Med 121:139–147

Blom AB, Brockbank SM, van Lent PL, van Beuningen HM, Geurts J, Takahashi N, van der Kraan PM, van de Loo FA, Schreurs BW, Clements K, Newham P, van den Berg WB (2009) Involvement of the Wnt signaling pathway in experimental and human osteoarthritis: prominent role of Wnt-induced signaling protein 1. Arthritis Rheum 60:501–512

Blom AB, van Lent PL, van der Kraan PM, van den Berg WB (2010) To seek shelter from the WNT in osteoarthritis? WNT-signaling as a target for osteoarthritis therapy. Curr Drug Targets 11:620–629

Burrage PS, Brinckerhoff CE (2007) Molecular targets in osteoarthritis: metalloproteinases and their inhibitors. Curr Drug Targets 8:293–303

Chen S, Leask A (2009) Wnt 10b activates the CCN2 promoter in NIH 3T3 fibroblasts through the Smad response element. J Cell Commun Signal 3:57–59

Chen Y, Abraham DJ, Shi-Wen X, Pearson JD, Black CM, Lyons KM, Leask A (2004) CCN2 (connective tissue growth factor) promotes fibroblast adhesion to fibronectin. Mol Biol Cell 15:5635–5646

Chen S, McLean S, Carter DE, Leask A (2007) The gene expression profile induced by Wnt 3a in NIH 3 T3 fibroblasts. J Cell Commun Signal 1:175–183

Elders MJ (2000) The increasing impact of arthritis on Public Health. J Rheumatol 27:6–8

French DM, Kaul RJ, D'Souza AL, Crowley CW, Bao M, Frantz GD, Filvaroff EH, Desnoyers L (2004) WISP-1 is an osteoblastic regulator expressed during skeletal development and fracture repair. Am J Pathol 165:855–867

Gao R, Brigstock DR (2006) A novel integrin alpha5beta1 binding domain in module 4 of connective tissue growth factor (CCN2/CTGF) promotes adhesion and migration of activated pancreatic stellate cells. Gut 55:856–862

Hoshijima M, Hattori T, Inoue M, Araki D, Hanagata H, Miyauchi A, Takigawa M (2006) CT domain of CCN2/CTGF directly interacts with fibronectin and enhances cell adhesion of chondrocytes through integrin alpha5beta1. FEBS Lett 580:1376–1382

Ijiri K, Nagayoshi R, Matsushita N, Tsuruga H, Taniguchi N, Gushi A, Sakakima H, Komiya S, Matsuyama T (2002) Differential expression patterns of secreted frizzled related protein genes in synovial cells from patients with arthritis. J Rheumatol 29:2266–2270

Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA et al (2008) Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 58:26–35

Lemaire R, Farina G, Bayle J, Dimarzio M, Pendergrass SA, Milano A, Perbal B, Whitfield ML, Lafyatis R (2010) Antagonistic effect of the matricellular signaling protein CCN3 on TGF-beta- and Wnt-mediated fibrillinogenesis in systemic sclerosis and Marfan syndrome. J Invest Dermatol 130:1514–1523

Lin CG, Leu SJ, Chen N, Tebeau CM, Lin SX, Yeung CY, Lau LF (2003) CCN3 (NOV) is a novel angiogenic regulator of the CCN protein family. J Biol Chem 278:24200–24208

Lützner J, Kasten P, Günther KP, Kirschner S (2009) Surgical options for patients with osteoarthritis of the knee. Nat Rev Rheumatol 5:309–316

Nakamura Y, Nawata M, Wakitani S (2005) Expression profiles and functional analyses of Wnt-related genes in human joint disorders. Am J Pathol 167:97–105

Oliviero F, Ramonda R, Punzi L (2010) New horizons in osteoarthritis. Swiss Med Wkly 140:w13098. doi:10.4414/smw.2010.13098

Ono M, Inkson CA, Kilts TM, Young MF (2010) WISP-1/CCN4 regulates osteogenesis by enhancing BMP-2 activity. J Bone Miner Res. 2010 Aug 3. [Epub ahead of print]

Pennica D, Swanson TA, Welsh JW, Roy MA, Lawrence DA, Lee J, Brush J, Taneyhill LA, Deuel B, Lew M, Watanabe C, Cohen RL, Melhem MF, Finley GG, Quirke P, Goddard AD, Hillan KJ, Gurney AL, Botstein D, Levine AJ (1998) WISP genes are members of the connective tissue growth factor family that are up-regulated in wnt-1-transformed cells and aberrantly expressed in human colon tumors. Proc Natl Acad Sci USA 95:14717–14722

Si W, Kang Q, Luu HH, Park JK, Luo Q, Song WX, Jiang W, Luo X, Li X, Yin H, Montag AG, Haydon RC, He TC (2006) CCN1/Cyr61 is regulated by the canonical Wnt signal and plays an important role in Wnt3A-induced osteoblast differentiation of mesenchymal stem cells. Mol Cell Biol 26:2955–2964