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The role of Dickkopf-1 in joint remodeling and fibrosis: A link connecting spondyloarthropathies and scleroderma?

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ABSTRACT

Background: Dickkopf-1 (Dkk-1) is a soluble inhibitor of the canonical Wnt pathway, which plays critical roles in embryonic development. Evidence suggests that this molecule regulates several aspects of both bone biology and fibrosis.
Objectives: To provide an overview of our current knowledge of the role of Dkk-1 in joint remodeling and fibrosis.
Methods: We performed an electronic search (Medline) using the following key words: Dickkopf-1 (or Dkk-1), new bone formation, joint remodeling, ankylosing spondylitis, systemic sclerosis (or scleroderma), and fibrosis, supplemented by a manual search of references from retrieved articles.
Results: Dkk-1 is a master regulator of joint remodeling in animal models of arthritis shifting the balance toward new bone formation when its expression is decreased and toward erosion/joint destruction when its expression is increased. In humans, evidence suggests that Dkk-1 may be dysfunctional in patients with ankylosing spondylitis, a prototype bone forming disease. Moreover, data from animal models indicate that Dkk-1 has a protective role against fibrosis in several organs. Recent data suggest that inhibiting the canonical Wnt pathway by overexpression of Dkk-1 could be a way to target TGF-β signaling in fibrotic diseases. Finally, B-cell depletion therapy in systemic sclerosis may exert its effects through TGF-β dependent upregulation of Dkk-1.
Conclusions: Dkk-1 appears to play a crucial role in both joint remodeling/ectopic ossification and fibrosis, and may be a prospective therapeutic modality for fibrotic diseases or diseases characterized by pathologic joint remodeling.

Introduction

Dickkopf-1 (Dkk-1) is a soluble inhibitor of the canonical Wnt pathway, a pathway controlling important processes and functions, such as embryonic development and stem-cell management. Evidence suggests that this molecule regulates several aspects of both bone biology and fibrosis. Dkk-1 has been recognized as a key player in animal models of arthritis and joint damage with increased levels linked to bone resorption and decreased levels linked to new bone formation [1]. It has recently been shown that inhibition of the canonical Wnt signaling by Dkk-1 prevents experimental fibrosis [2]. Spondyloarthropathies are a heterogeneous group of diseases that are characterized by new bone formation in the form of ectopic ossification. Systemic sclerosis is the prototype multisystem fibrotic disease. Surprisingly, recent data indicate that these diseases, despite their striking differences, may have something in common; ectopic ossification and fibrosis are both related to reactivation of developmental pathways. Developmental pathways are mainly active during embryogenesis and their main function is to orchestrate growth and development [3,4]. However, these pathways can be activated during adult life as well, mainly as a reaction to tissue injury. A great amount of experimental evidence suggests that the developmental pathways have a significant role in homeostasis, maintenance, healing, and fibrosis [5–7]. The best studied developmental pathway is the Wnt/β-catenin, also called the canonical Wnt pathway. The Wnt proteins are a family of 19 secreted factors, which act as ligands to activate the pathway. Beta-catenin operates as a transcriptional coactivator of the T-cell factor (TCF) family of DNA-binding proteins and processes signals from various Wnts to modulate gene transcription. Wnts bind to their cell surface receptors

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Frizzled (Fz) and LRP5/6 to activate the canonical Wnt signaling pathway. In the absence of Wnt signals, a "destruction" complex comprising APC, axin, glycogen synthase kinase 3β (GSK-3β) and caseine kinase, and phosphorylates β-catenin leading to its degradation. Binding of Wnts to a coreceptor complex that consists of LRP5/6 and a member of frizzled family of proteins destabilizes the "destruction complex" and prevents β-catenin degradation. Unphosphorylated β-catenin accumulates and translocates to the nucleus, where it binds to the family of TCF proteins and stimulates the transcription of target genes [8–10]. The pathway is regulated by inhibitory molecules, such as Dkk-1. The prevailing view is that Dkk-1 binds LRP5/6 and Kremen, resulting in rapid endocytosis of the complex, removal of LRP5/6 receptors from the cell membrane and inhibition of the pathway [11]. However, there is also evidence suggesting that Dkk-1 competes directly with Wnt proteins for LRP6 binding, thereby disrupting Wnt-induced Fz-LRP6 complex formation [12,13]. Abundant evidence suggests that Dkk-1 is a strong inhibitor of the Wnt pathway, but exactly how this molecule exerts its inhibitory action is still not completely understood. The first evidence connecting the Wnt pathway to osteoblastogenesis came from genetic disorders of altered skeletal mass. Mutations of the low-density lipoprotein receptor-related protein 5 (LRP5) create gene gain or loss of function receptors that are resistant to normal regulatory mechanisms and cause high or low bone density, respectively [14,15]. A role for Wnt/β-catenin signaling in fibroproliferative disorders was initially supported by the high rate of mutations detected in the genes encoding β-catenin and its negative regulator adenomatosis polyposis coli (APC) in aggressive fibromatosis [16]. Since then, data have been accumulating indicating that excessive Wnt/β-catenin signaling can promote aspects of both osteoblastogenesis and fibrosis across several tissues and cell systems. Recently, an additional view has emerged from research. Data derived from animal models of fibrosis indicate that Dkk-1 may have a suppressive effect on platelet derived growth factor (PDGF), transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF) signaling pathways; this effect is Wnt/β-catenin independent [17]. Therefore, Dkk-1 should not be regarded solely as a specific Wnt pathway inhibitor, but may act on other signaling pathways as well. The canonical Wnt pathway and the function of Dkk-1 are diagrammatically shown in Figure 1. Dkk-1 is soluble molecule, and therefore it can be readily measured in peripheral blood. Serum Dkk-1 levels can be measured by classical sandwich ELISA assays (from now on referred to as circulating Dkk-1). However, its biological activity is better determined by functional ELISA assays, with human LRP6-coated plates, measuring the ability of Dkk-1 to bind LRP6 receptor (from now on referred to as functional Dkk-1).

In this article we aimed at providing an overview of the role of Dkk-1 in joint remodeling and fibrosis.

Methods

We performed an electronic search (Medline) using the following key words: Dickkopf-1 (or Dkk-1), new bone formation, joint remodeling, ankylosing spondylitis, systemic sclerosis (or scleroderma), and fibrosis. The combinations used were Dickkopf-1 (or Dkk-1) with any one of the above key words. The only limit set was English language. The computerized search was supplemented by a manual one on the reference lists of the retrieved articles.

The search identified 187 articles; following duplicate removal, 117 articles remained and were screened for eligibility. Overall, 58 articles were excluded, because they were irrelevant to study subject; the remaining 59 articles were evaluated and finally 38 were selected and included in the analysis based on relevance to study subject and scientific interest. The relevant flowchart is presented in Figure 2.

The role of Dkk-1 in joint remodeling

Data from animal models

Dkk-1 as a key player in animal models of arthritis and joint damage. Diarra et al. [1] explored the role of Dkk-1 in joint remodeling. The authors hypothesized that Wnt activation in the inflamed joint might be blocked by the pathway inhibitor Dkk-1.

They used several mouse models of inflammatory arthritis, including the TNFα transgenic mouse, and found that Dkk-1 is overexpressed in arthritic erosive joints. Dkk-1 blockade with anti-Dkk1 monoclonal antibody (mAb) in these mice led not only to protection against erosions, but to osteophyte formation, as well. Anti-Dkk1 mAb treatment had no effect on inflammation indicating that in this model inflammation and joint destruction are uncoupled. The authors suggest that Dkk-1 is a master regulator of joint remodeling shifting the balance toward new bone formation when its expression is decreased and toward erosion/joint destruction when its expression is increased. This was the first study to indicate the pivotal role of Dkk-1 in the process of joint remodeling in animal models of inflammatory arthritis.

Walsh et al. [18] tried to explore the capacity of osteoblasts to form mineralized bone within the arthritic bone microenvironment. Using dynamic bone histomorphometry in a murine model of inflammatory arthritis, they found that osteoblast activity was compromised and did not compensate for bone loss at sites of inflammation and erosion. Reduced osteoblast activity was linked to DKK1 upregulation; DKK1 mRNA expression exhibited a 5-fold upregulation in murine arthritic synovial tissues compared with non-arthritic mice at a time point when inflammation and focal erosion peaked. It is known that joint inflammation leads to destruction by enhancement of osteoclastogenesis. However, these data suggest that inflammation within the arthritic bone microenvironment is associated with impaired osteoblast function as well. The inflammation-mediated suppression of osteoblastogenesis is linked to Wnt pathway inhibition by upregulation of inhibitors such as Dkk-1.

The role of Dkk-1 in sacroiliac fusion, a hallmark of spondyloarthropathies, was explored by Uderhardt et al. They used TNFα transgenic mice that develop bilateral sacroiliitis with subsequent erosions, but not spontaneous ankylosis of the sacroiliac joints. Treatment of these mice with anti-Dkk1 mAb led to attenuation of erosions and fusion of sacroiliac joints [19]. Immunohistochemistry revealed β-catenin upregulation within the sacroiliac joints, on Dkk-1 blockade, suggesting that Dkk-1 inhibition caused enhancement of the Wnt signaling pathway and led to new bone formation and ankylosis. These data indicate that Dkk-1 is not only a key regulator of joint remodeling in peripheral joints but it is actively involved in new bone formation in the axial skeleton, a characteristic feature of spondyloarthropathies.

Data from humans

Since the role of Dkk-1 in joint remodeling has been established in animal models, several investigators have assessed Dkk-1 levels in humans focusing on patients with diseases characterized by pathologic joint remodeling such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Diarra et al. [1] were the first to assess functional Dkk-1 levels in patients with RA, AS, and healthy subjects. Patients with RA had higher functional Dkk-1 levels compared with healthy controls; moreover they had increased Dkk-1 expression in the inflamed synovium. In sharp contrast, patients with AS had decreased functional Dkk-1 levels compared