pISSN: 2093-940X, eISSN: 2233-4718
Journal of Rheumatic Diseases Vol. 29, No. 1, January, 2022
https://doi.org/10.4078/jrd.2022.29.1.1

Editorial

The Long, Dynamic Journey to the Elucidation of the Links Between Inflammation, Ectopic Bone Formation, and Wnt Signaling in Ankylosing Spondylitis

Seong-Ryul Kwon, M.D., Ph.D.
Rheumatism Center, Department of Internal Medicine, Inha University College of Medicine, Incheon, Korea

Ankylosing spondylitis (AS) is a chronic inflammatory disorder characterized by inflammation of the axial skeleton and sacroiliac joints and to a lesser extent by peripheral arthritis and the involvement of some extra-articular organs comprising the gastrointestinal tract, eyes, cardiovascular system, and entheses [1]. Characteristic lesions of the skeletal system include ectopic new bone formation and syndesmophytes [2,3]. Ectopic new bone formation may impair spinal mobility, which limits daily activities and reduces quality of life [4,5]. Therefore, suppressing skeletal damage in AS is an important treatment goal.

The question as to whether inflammation and ectopic new bone formation are related or not in AS is long-standing, and hitherto remains unresolved. The first theory is that inflammation and ectopic new bone formation are related. It is postulated inflammation is initially triggered by mechanical stress or infection, leading to the bony catabolic process. Subsequently, as inflammation decreases either rapidly or slowly, the catabolic bony process is changed to an anabolic response, which results in characteristic reactive new bone formation [6,7]. Another theory is that inflammation and new bone formation are unrelated and that some unknown factors independently trigger inflammation and new bone formation [8]. However, if inflammation is associated with ectopic new bone formation, ectopic new bone formation would probably be inhibited by a strong anti-inflammatory treatment (for example, anti-tumor necrosis factor [TNF] α therapy) at an early stage. On the other hand, if inflammation and ectopic new bone formation are independently triggered by certain factors, we must find and inhibit those factors to prevent ectopic new bone formation.

Magnetic resonance imaging (MRI) studies have shown there is an increased likelihood of ectopic new bone formation on follow up MRI after 2 years in the initially inflamed vertebral corner [9,10]. Furthermore, in these MRI studies, ectopic new bone formation occurred more frequently in the inflammation subsided vertebral corners than in those showing continued inflammation [9,11]. According to another MRI study, ectopic new bone formation occurred at the same location after fatty metaplasia at the vertebral corner [12]. Importantly, it has been suggested that systemic inflammation, represented by acute phase reactant levels, could predict radiologic progression of vertebrae [13,14].

Reported results conflict as to whether ectopic bony progression can be inhibited by anti-TNF α therapy. Early large-scale clinical studies showed that anti-TNF α agents could not inhibit bony progression [15-17]. These studies compared patients treated with anti-TNF α agents during clinical trials and the patients with spinal X-rays stored in the cohort without anti-TNF α agents during same period. However, recent long-term studies have reported that anti-TNF α agents inhibit ectopic bony progression [18-20]. In the earlier large-scale clinical studies [15-17], patients were treated with an anti-TNF α agent for 2 years and compared with a historical cohort group of nearly 200 patients treated without anti-TNF α agent, whereas the recent long-term studies [18-20] in-

Received : October 26 2021, **Revised** : December 4, 2021, **Accepted** : December 5, 2021

Corresponding to : Seong-Ryul Kwon http://orcid.org/0000-0003-1262-2790
Rheumatism Center, Department of Internal Medicine, Inha University College of Medicine, 27 Inhang-ro, Jung-gu, Incheon 22332, Korea. E-mail : rhksr@inha.ac.kr

cluded patients treated with an anti-TNF α agent in the real world for 8 to 18 years.

Wnt signaling and the role of Dickkopf (DKK) are also important topics related to ectopic bone formation in AS is. Reports regarding the roles of DKK in bone development and homeostasis diverge. Some have reported that DKK, which acts as an inhibitor of Wnt in canonical Wnt signaling, inhibits bone development. Diarra et al. [21] investigated the role of DKK in rheumatoid arthritis and AS, and found DKK1 inhibition caused the bone-destructive pattern observed in a mouse model of rheumatoid arthritis to a bone forming pattern than wild-type controls. Furthermore, DKK1$^{+/-}$ mice exhibited significantly greater bone formation and bone mass [22], and DKK1 inhibited bone growth and repair during the growth stage and adolescence, but not in old age of rodents [23]. On the other hand, DKK2 is known to be a positive regulator of osteoblast maturation, and DKK2 deficiency weakens bone mineralization, increases bone resorption, and caused osteopenia [24].

A recent article by Jo et al. [25] published in the *Journal of Rheumatic Diseases* provide a clue to the underlying mechanism of inflammation, bony ankylosis, and DKK1. They compared the serum levels of DKK1 between 103 patients with AS and 30 healthy controls (HCs). Furthermore, they evaluated the impact of TNF α on DKK1 expression in human primary spinal enthesis cells using various molecular biology techniques and bone formation indicators. The data demonstrated that 1) AS patients showed higher serum DKK1 levels than HCs after adjusting for age, 2) TNF α treatment promoted bone formation and DKK1 expression in both control enthesis cells and those of AS, 3) enhanced bone formation by TNF α was pronounced in AS-enthesis than those of controls, 4) TNF α induced nuclear factor- κ B (NF- κ B) activation upregulates the DKK1 transcript level, 4) NF- κ B inhibitor led to downregulate DKK1 expression in the enthesis, 5) finally, DKK1 overexpression promoted bone formation in enthesis.

It was concluded TNF α induced DKK1 expression in enthesis through NF- κ B activation. Compared with previous studies, this study reported that new bone formation was achieved by TNF α associated with inflammation in AS, and that DKK1 played a role as a positive regulator, not negative regulator of bone formation. Regarding conflicting reports of DKK on bone formation in families, DKK2 acts as a positive regulator of osteoblast maturation [24]. Furthermore, Zhou et al. [26] reported that miR-483-3p induced DKK2 to increase bone formation when differentiating from pre-osteoblast to mature osteoblast. These apparently surprising results fit well with the concept proposed by Rodda and McMahon [27] that Wnt signaling acts as a negative regulator when osteoblasts have differentiated into mature osteoblasts. In the study by Jo et al. [25], the authors revealed that TNF α -induced DKK1 expression through NF- κ B activation, therefore if they identify what changes occur during TNF α treatment in DKK1 knockout conditions, they could provide solid evidence about TNF α -induced DKK1 expression through NF- κ B activation.

The study by Jo et al. [25] is important in many ways. First, it improves our understating of the underlying molecular mechanisms of bony ankylosis and enthesis in AS, especially the role of the TNF-NF- κ B-DKK1 axis. Second, it extended the previously reported functional role of DKK1 in bone formation [28,29]. Third, it provided novel insights into the molecular linkage between TNF α and DKK1.

This article has broadened fundamental understanding of bone formation and the pathogenesis of radiographic progression in AS. In addition, this article suggests that TNF α -mediated DKK1 plays a role in the radiographic progression of AS. Further studies are needed to identify the molecular mechanisms responsible, and clinical studies to elucidate the nature of the links between Wnt signaling, inflammation and bone formation.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERRENCES

1. Park PR, Jo S, Jin SH, Kim TJ. MicroRNA-10b plays a role in bone formation by suppressing interleukin-22 in ankylosing spondylitis. J Rheum Dis 2020;27:61-7.
2. Baraliakos X, Listing J, Rudwaleit M, Haibel H, Brandt J, Sieper J, et al. Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. Ann Rheum Dis 2007;66:910-5.
3. van Tubergen A, Ramiro S, van der Heijde D, Dougados M, Mielants H, Landewé R. Development of new syndesmophytes and bridges in ankylosing spondylitis and their predictors: a longitudinal study. Ann Rheum Dis 2012;71:518-23.
4. Landewé R, Dougados M, Mielants H, van der Tempel H, van der Heijde D. Physical function in ankylosing spondylitis is independently determined by both disease activity and

radiographic damage of the spine. Ann Rheum Dis 2009; 68:863-7.
5. Machado P, Landewé R, Braun J, Hermann KG, Baker D, van der Heijde D. Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. Ann Rheum Dis 2010; 69:1465-70.
6. Schett G, Rudwaleit M. Can we stop progression of ankylosing spondylitis? Best Pract Res Clin Rheumatol 2010;24: 363-71.
7. Sieper J, Appel H, Braun J, Rudwaleit M. Critical appraisal of assessment of structural damage in ankylosing spondylitis: implications for treatment outcomes. Arthritis Rheum 2008;58:649-56.
8. Lories RJ, Luyten FP, de Vlam K. Progress in spondylarthritis. Mechanisms of new bone formation in spondyloarthritis. Arthritis Res Ther 2009;11:221.
9. Maksymowych WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Østergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. Arthritis Rheum 2009;60:93-102.
10. van der Heijde D, Machado P, Braun J, Hermann KG, Baraliakos X, Hsu B, et al. MRI inflammation at the vertebral unit only marginally predicts new syndesmophyte formation: a multilevel analysis in patients with ankylosing spondylitis. Ann Rheum Dis 2012;71:369-73.
11. Pedersen SJ, Chiowchanwisawakit P, Lambert RG, Østergaard M, Maksymowych WP. Resolution of inflammation following treatment of ankylosing spondylitis is associated with new bone formation. J Rheumatol 2011; 38:1349-54.
12. Chiowchanwisawakit P, Lambert RG, Conner-Spady B, Maksymowych WP. Focal fat lesions at vertebral corners on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis. Arthritis Rheum 2011;63:2215-25.
13. Poddubnyy D, Haibel H, Listing J, Märker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum 2012;64:1388-98.
14. Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Märker-Hermann E, Zeidler H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70:1369-74.
15. van der Heijde D, Landewé R, Baraliakos X, Houben H, van Tubergen A, Williamson P, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum 2008;58:3063-70.
16. van der Heijde D, Landewé R, Einstein S, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum 2008;58:1324-31.
17. van der Heijde D, Salonen D, Weissman BN, Landewé R, Maksymowych WP, Kupper H, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther 2009;11:R127.
18. Haroon N, Inman RD, Learch TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013;65:2645-54.
19. Koo BS, Oh JS, Park SY, Shin JH, Ahn GY, Lee S, et al. Tumour necrosis factor inhibitors slow radiographic progression in patients with ankylosing spondylitis: 18-year real-world evidence. Ann Rheum Dis 2020;79:1327-32.
20. Park JW, Kim MJ, Lee JS, Ha YJ, Park JK, Kang EH, et al. Impact of tumor necrosis factor inhibitor versus nonsteroidal antiinflammatory drug treatment on radiographic progression in early ankylosing spondylitis: its relationship to inflammation control during treatment. Arthritis Rheumatol 2019;71:82-90.
21. Diarra D, Stolina M, Polzer K, Zwerina J, Ominsky MS, Dwyer D, et al. Dickkopf-1 is a master regulator of joint remodeling. Nat Med 2007;13:156-63.
22. Morvan F, Boulukos K, Clément-Lacroix P, Roman Roman S, Suc-Royer I, Vayssière B, et al. Deletion of a single allele of the Dkk1 gene leads to an increase in bone formation and bone mass. J Bone Miner Res 2006;21:934-45.
23. Li X, Grisanti M, Fan W, Asuncion FJ, Tan HL, Dwyer D, et al. Dickkopf-1 regulates bone formation in young growing rodents and upon traumatic injury. J Bone Miner Res 2011;26:2610-21.
24. Li X, Liu P, Liu W, Maye P, Zhang J, Zhang Y, et al. Dkk2 has a role in terminal osteoblast differentiation and mineralized matrix formation. Nat Genet 2005;37:945-52.
25. Jo S, Nam B, Lee YL, Park H, Weon S, Choi SH, et al. The TNF-NF-κB-DKK1 axis promoted bone formation in the enthesis of ankylosing spondylitis. J Rheum Dis 2021;28: 216-24.
26. Zhou B, Peng K, Wang G, Chen W, Liu P, Chen F, et al. miR-483-3p promotes the osteogenesis of human osteoblasts by targeting Dikkopf 2 (DKK2) and the Wnt signaling pathway. Int J Mol Med 2020;46:1571-81.
27. Rodda SJ, McMahon AP. Distinct roles for Hedgehog and canonical Wnt signaling in specification, differentiation and maintenance of osteoblast progenitors. Development 2006; 133:3231-44.
28. Jo S, Yoon S, Lee SY, Kim SY, Park H, Han J, et al. DKK1 induced by 1,25D3 is required for the mineralization of osteoblasts. Cells 2020;9:236.
29. Nam B, Park H, Lee YL, Oh Y, Park J, Kim SY, et al. TGFβ1 suppressed matrix mineralization of osteoblasts differentiation by regulating SMURF1-C/EBPβ-DKK1 axis. Int J Mol Sci 2020;21:9771.