Title: Anti-Sclerostin Antibody Therapy Prevents Post-Ischemic Osteonecrosis Bone Collapse via Interleukin-6 Association

【Key Points】
-In osteonecrosis of the femoral head, an increase in β-catenin and IL6 was observed in the transitional layer, indicating a link between osteonecrosis of the femoral head and the Wnt/β-catenin pathway.
-Consequently, administering anti-sclerostin antibodies, a medication for osteoporosis known to enhance the Wnt/β-catenin signal, resulted in the suppression of the osteoclastogenic cytokine IL-6. --This, in turn, inhibited the formation of osteoclasts and prevented the collapse of the bone end after necrosis.
The results of this study hold promise for application in the challenging treatment of idiopathic osteonecrosis of the femoral head.

【Summary】
A research group led by Dr. Yuto Ozawa, Yasuhiko Takegami and Professor Shiro Imagama has discovered in a mouse model of ischemic femoral condyle necrosis that administering anti-sclerostin antibodies, a drug for treating osteoporosis, prevents the collapse of the femoral condyle. Furthermore, it was found that the expression of IL-6 was reduced in the group treated with anti-sclerostin antibodies. This study indicates that anti-sclerostin antibodies can effectively modulate the Wnt/β-catenin signal and are associated with the expression of IL-6, potentially preventing the collapse of the femoral head in osteonecrosis.
Osteonecrosis of the femoral head is a severe condition leading to joint destruction characterized by the necrosis of cartilage and is classified as a specific disease. Treatment for osteonecrosis of the femoral head usually involves total hip arthroplasty, but the outcomes are not always satisfactory, especially in younger patients.
In this study, β-catenin and IL-6 staining of human femoral heads were first conducted, showing increased expression of β-catenin and IL-6 in the transitional layer. The study then administered anti-sclerostin antibodies to a mouse model of ischemic femoral condyle necrosis to examine the degree of condyle collapse, bone metabolism, and the effects on the Wnt/β-catenin signal. Histologically, the anti-sclerostin

antibodies led to early recovery from necrosis, a reduction in Empty lacunae characteristic of necrosis, and activation of the Wnt/β-catenin signal, suggesting a possible association with IL-6-mediated inflammation. Additionally, μCT scans demonstrated that in the ischemic femoral condyle necrosis model, the group treated with anti-sclerostin antibodies showed an increase in bone mass, prevention of condyle collapse, and improved compression strength.
This study suggests that anti-sclerostin antibodies could be useful in treating bone necrosis. The findings of this study will be published in the journal 'Bone'.

【Research Background】
Osteonecrosis of the femoral head can lead to joint destruction as it progresses. In Japan, the incidence rate of osteonecrosis of the femoral head is reported to be 1.9 cases per 100,000 people per year. Total hip arthroplasty is a common treatment for osteonecrosis of the femoral head, but the outcomes are often poor in patients under the age of 60. Joint-preserving treatments such as decompression therapy and medication treatments like bisphosphonates have been reported, but their efficacy is limited.

Osteonecrosis of the femoral head is said to be caused by chronic inflammation and is deeply associated with IL-6. Recently, it has been reported that activating the Wnt/β-catenin pathway can promote bone formation and inhibit bone resorption, suggesting its relevance in the treatment of osteonecrosis of the femoral head. Additionally, anti-sclerostin antibodies, which inhibit the action of sclerostin that deactivates the Wnt/β-catenin pathway, are garnering attention as osteoporosis drugs.

On the other hand, the interrelationship between IL-6 and the Wnt/β-catenin pathway in osteonecrosis of the femoral head is not yet understood. The purpose of this study is to investigate the relationship between osteonecrosis of the femoral head, the Wnt/β-catenin pathway, and IL-6, and to explore the potential for therapeutic intervention using anti-sclerostin antibodies in the treatment of osteonecrosis of the femoral head.

【Research summary】
Femoral heads were extracted from patients with osteonecrosis of the femoral head and from patients with osteoarthritis. These femoral heads were then stained for IL-6 and β-catenin. An increase in the expression of β-catenin and IL-6 was observed in the transitional layer. (See Figure 1)

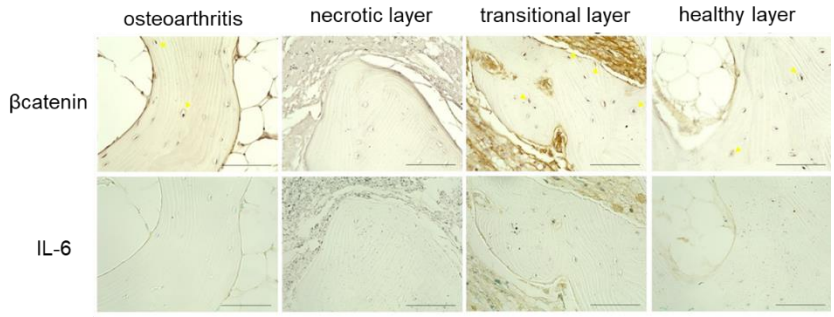

Figure1　osteoarthritis and osteonecrosis

We compared the timeline of recovery from ischemic bone necrosis using a mouse model of femoral condyle necrosis between groups treated with anti-sclerostin antibodies and vehicle (Veh) groups. In the group treated with anti-sclerostin antibodies, a reduction in necrotic Empty lacunae and the appearance of bone trabecular structure were observed at 4 weeks. (See Figure 2)

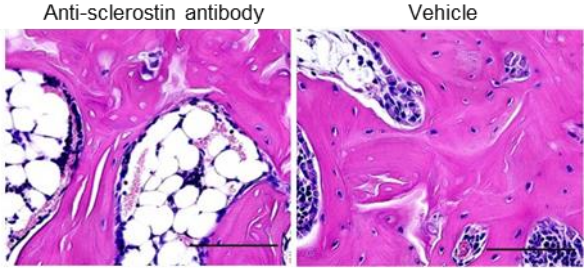

Figure2 HE staining at 4 weeks post-surgery

We performed RT-PCR on the femoral condyle using a mouse model of femoral condyle necrosis. In the group treated with anti-sclerostin antibodies, an increase in β-catenin and a decrease in IL-6 were observed on the ischemic necrosis side. (See Figure 3) Similarly, immunohistochemical staining also showed suppression of IL-6.

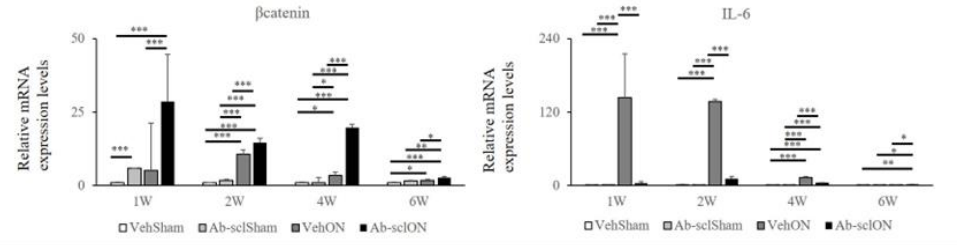

Figure3 RT-PCR

We conducted TRAP staining, which is used to stain osteoclasts. At two weeks post-surgery, a significant reduction in osteoclasts was observed in the group treated with anti-sclerostin antibodies on the ischemic necrosis side. (See Figure 4)

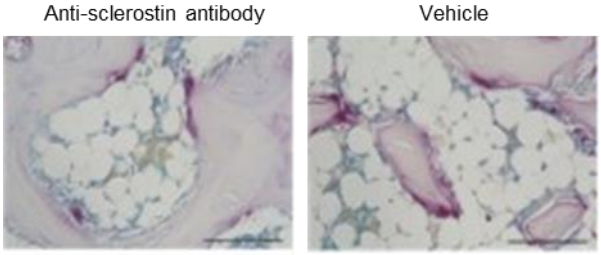

Figure4 TRAP staining at 2 week post-surgery

In μCT scans, an increase in BV/TV (Bone Volume/Total Volume) was observed in the group treated with anti-sclerostin antibodies on the ischemic necrosis side, for both the necrosis surgery side and the Sham surgery side. Additionally, at 6 weeks post-surgery, inhibition of femoral condyle collapse was observed in the group treated with anti-sclerostin antibodies. (See Figure 5)

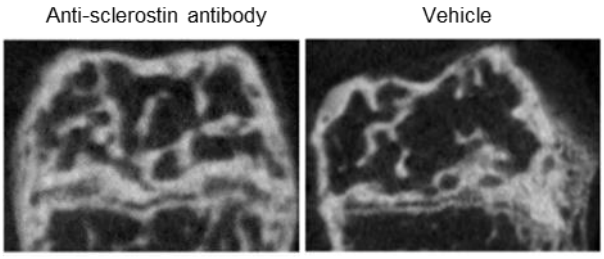

Figure5 μCT at 6 week post-surgery

【Future Developments】

This study found that anti-sclerostin antibodies are associated with the expression of IL-6 in the ischemic necrosis of the femoral condyle, promoting the reduction of Empty lacunae and decreasing osteoclasts, thereby inhibiting the collapse of the femoral condyle. This suggests that

Evenity, currently used as an osteoporosis drug and an anti-sclerostin antibody, could potentially be a treatment for osteonecrosis of the femoral head. Future studies, such as prospective research on the use of Evenity in patients with osteonecrosis of the femoral head, are considered necessary.

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