News Release

Title

Potential of novel treatment approaches to target cellular senescence in the osteonecrosis of the femoral head

Key Points

•Osteonecrosis of the femoral head (ONFH) is a disease that causes loss of hip function due to ischemia.

• We have clarified the involvement of cellular senescence in ONFH.

•We found that the accumulation of senescent cells and secretion associated with cellular senescence (SASP) occurred not only in the necrotic region but also in the transitional region of the femoral head.

•In a mouse ischemic osteonecrosis model, administration of mesenchymal stem cell conditioned medium (MSC-CM) inhibited cellular senescence and suppressed bone collapse.

• Novel treatments targeting cellular senescence in ONFH are expected.

Summary

A research group led by Dr. Masanori Okamoto, Associate Professor Hiroaki Nakashima, Professor Shiro Imagama (Department of Orthopaedic Surgery, Nagoya University Graduate School of Medicine), Professor Hideharu Hiharu, and Assistant Professor Kiyoshi Sakai (Department of Oral and Maxillofacial Surgery, Nagoya University Graduate School of Medicine) has newly discovered that that cellular senescence is involved in osteonecrosis of the femoral head (ONFH).

ONFH is a disease that causes ischemic necrosis of the femoral head of the bone and loss of hip function as the necrotic bone tissue collapses. Its pathogenesis has not yet been fully elucidated.

In this study, by analyzing bone heads removed from patients with ONFH at the time of surgery, it became clear that senescent cells accumulated in the transitional region between the healthy and necrotic region inside the head. Furthermore, senescent cells release various factors that cause inflammation, a phenomenon called SASP, which was found in the transitional region of ONFH. Experiments using a mouse model of ischemic osteonecrosis showed that SASP prevented bone collapse by suppressing cellular senescence.

The results of this study are expected to lead to the clinical development of cellular senescence as a potential new therapeutic target for ONFH.

This research was published online in the British scientific journal, "Scientific Reports," on February 9, 2024.

Research Background

ONFH is bone death associated with circulatory disruption. ONFH develops when the bone head collapses. This disorder eventually progresses to secondary osteoarthritis. In the United States, nearly 20,000 new cases are diagnosed annually. Its pathogenesis is associated with dyslipidemia, thrombosis, cell death, oxidative stress, and damage-associated molecular patterns but has not yet been fully elucidated. Osteotomy and total hip arthroplasty are the currently available treatments. Hence, a therapeutic agent that efficaciously treats ONFH with minimal invasion is required.

In recent years, attention has focused on the fact that cellular senescence and SASP are associated with atherosclerosis, type 2 diabetes mellitus, renal failure, osteoarthritis, and osteoporosis. This research group previously elucidated the involvement of cellular senescence in drug-induced osteonecrosis of the jaw (Watanabe et al., 2020).

In this study, this research group wanted to investigate the relationship between ONFH, a form of osteonecrosis, and cellular senescence. They also investigated the possibility of treating inhibitory osteonecrosis through an approach that regulates cellular senescence.

Research Results

The research group analyzed femoral heads removed at the time of surgery from patients diagnosed with ONFH. X-gal staining of the femoral head specimen showed a band of staining inside femoral head, indicating senescent cells (Figure 1). This band was found to correspond to the transitional region at the border between the necrotic regio and the healthy region in ONFH. Histological and gene expression analysis revealed that cellular senescence occurred not only in the necrotic region but also in the transitional region, and that the SASP factor was also highly expressed.

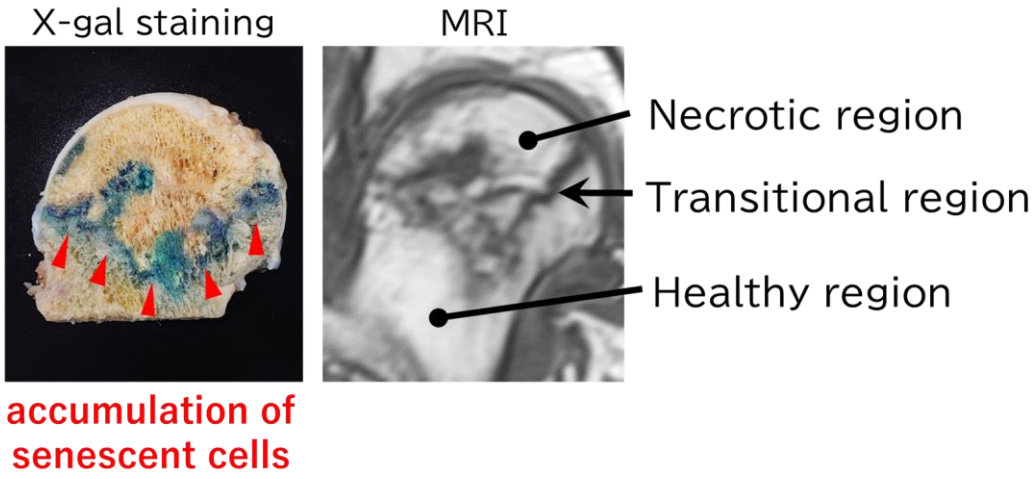

Figure 1. Photograph of the coronal section of a human femoral head stained with X-gal and MRI image. The band-shaped area-stained blue by X-gal was consistent with the transition region indicated by the T1-weighted MRI.

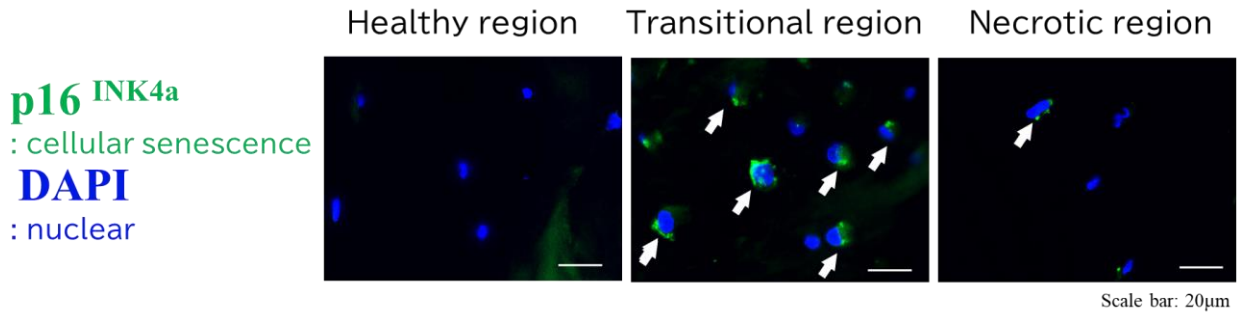

Figure 2. Immunofluorescence
The transitional region contains many p16ink4a-positive cells, one of the most common markers of cellular senescence.

Next, the research group performed surgery to cauterize blood vessels feeding the femur in 12-week-old mice, which interrupts blood flow and causes osteonecrosis in a mouse model of inhibited osteonecrosis. To investigate whether osteonecrosis can be treated by controlling cellular senescence in the ischemic osteonecrosis model, human-derived mesenchymal stem cell culture supernatant (MSC-CM) was administered 24 hours after surgery. The activity of cellular senescence-associated β-galactosidase was upregulated after ischemic surgery. However, administration of MSC-CM suppressed the activity, indicating that cellular senescence was suppressed. MSC-CM did not suppress ischemia-induced cell death. Nevertheless, it prevented cellular senescence in the bone tissue, promoted bone formation, and prevented bone collapse at 6 weeks after surgery. Therefore, the regulation of cellular senescence may be a therapeutic target for ONFH.

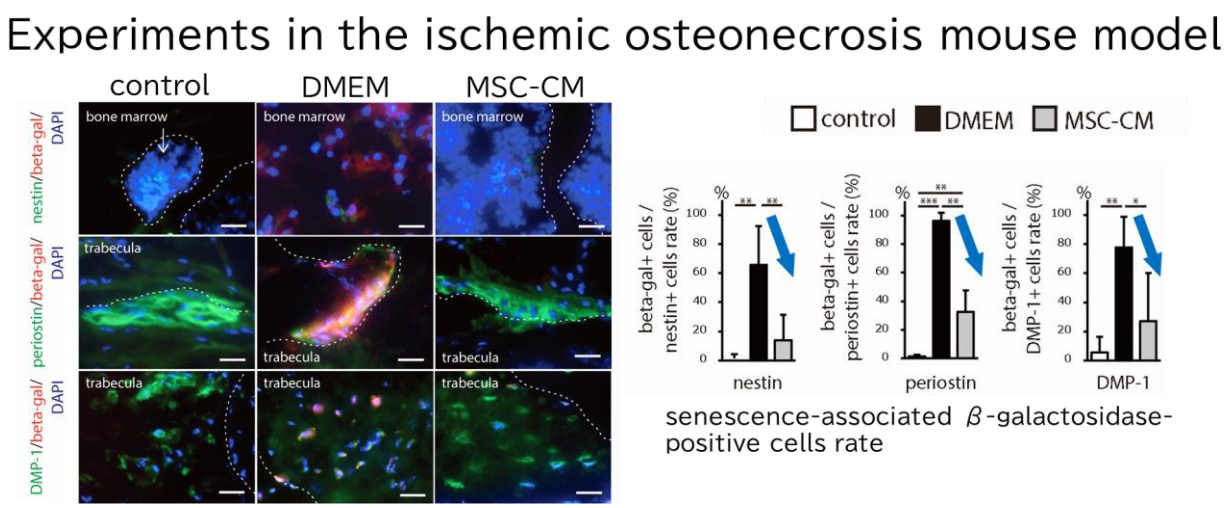

Figure 3. Activity of senescence-associated β-galactosidase

Compared to controls without ischemia surgery, cellular senescence was observed after ischemia surgery when only culture medium (DMEM) was administered, whereas cellular senescence was suppressed when MSC-CM was administered.

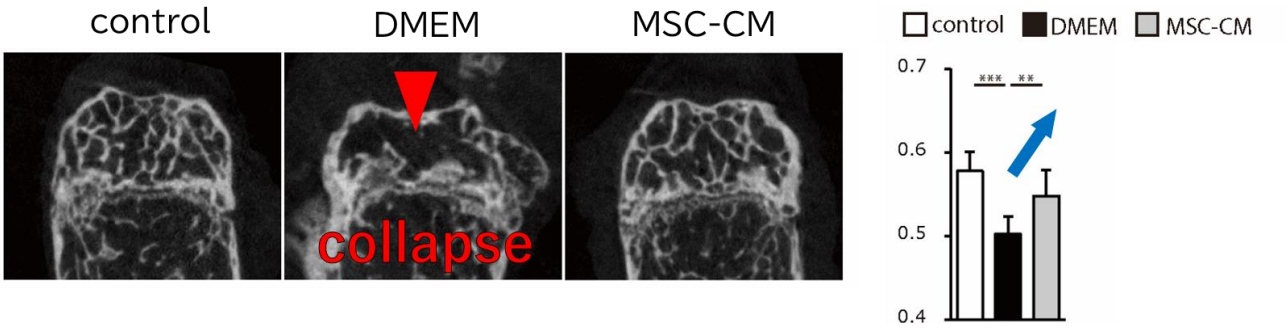

Figure 4. micro-CT

Although the bone collapse was caused by ischemic osteonecrosis, administration of MSC-CM prevented the collapse.

Research Summary and Future Perspective

The current research demonstrated the involvement of cellular senescence in ONFH, a form of ischemic bone necrosis, and further demonstrated that suppressing cellular senescence associated with ischemic bone necrosis could prevent bone collapse. Prevention of femoral head collapse is a therapeutic goal in femoral head necrosis, thus the suppression of collapse observed in the mouse experiments of this study is considered significant. In the future, it is expected that this will lead to new treatment strategies to prevent collapse of femoral head and avoid surgery.

Publication

Masanori Okamoto, Hiroaki Nakashima, Kiyoshi Sakai, Yasuhiko Takegami, Yusuke Osawa, Junna Watanabe, Sadayuki Ito, Hideharu Hibi, Shiro Imagama. Cellular senescence is associated with osteonecrosis of the femoral head while mesenchymal stem cell conditioned medium inhibits bone collapse. *Scientific Reports*, published online on February 9, 2024.
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Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Sci_240215.pdf