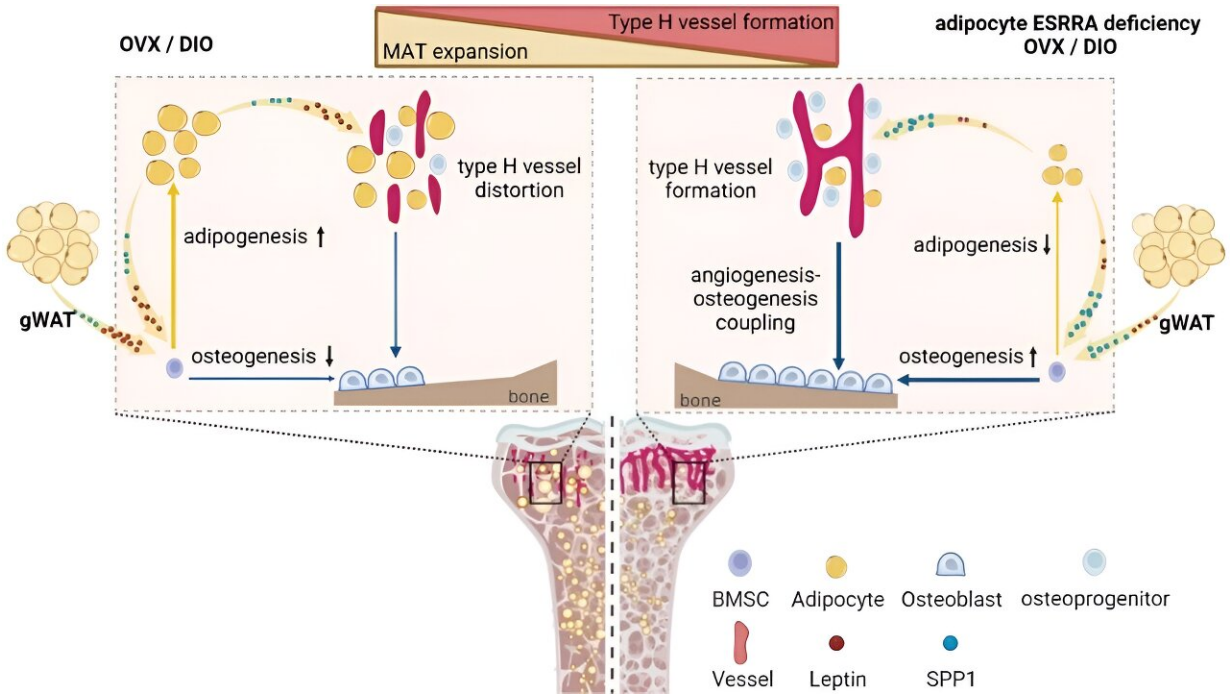
Medical Xpress

Novel mechanism for targeting bone marrow adipocytes to prevent bone loss

June 28 2024



Schematic diagram showing adipocyte ESRRA deficiency preserves osteogenesis and vascular formation in adipocyte-rich bone marrow via oppositely modulating lepin and SPP1. Credit: Guan Min

Bone marrow adipocytes (BMAds) are situated within the bone microenvironment, in close proximity to bone cells, vascular structures, and hematopoietic tissues. The shift of bone marrow stromal/stem cells (BMSCs) lineage towards committed adipogenic progenitors at the

expense of osteoprogenitors is driven by abnormal signaling within the bone microenvironment due to pathophysiological conditions.

However, the precise mechanisms underlying excessive BMAds, particularly in response to pathophysiological conditions, in mediating cellular communication among bone-resident cells remain unclear.

Recently, a research team led by Prof. Guan Min from the Shenzhen Institute of Advanced Technology (SIAT) of the Chinese Academy of Sciences has revealed that the absence of estrogen-related receptor α (ESRRA) in adipocytes, leads to changes in the expression of secreted factors that have synergistic effects on BMSCs fate determination and vascular endothelial cells angiogenesis. These indicate that targeting ESRRA in adipocytes could be a potential therapeutic target for osteoporosis.

The study was published in *Nature Communications* on May 4.

In this study, researchers found that adipocyte-specific ESRRA knockout rescues bone loss and type H vessel distortion, as well as inhibits marrow adiposity in mice induced by ovariectomy (OVX) or diet-induced obesity (DIO).

Experimental results showed that adipocyte ESRRA interferes with the signaling of 17-estradiol and estrogen receptor alpha, resulting in the transcriptional repression of secreted phosphoprotein 1 (Spp1). Consequently, the release of SPP1 from ESRRA-deficient adipocytes enhances endothelial cells migration and restores type H vessels formation in mice induced by OVX or DIO.

Additionally, ESRRA positively modulates leptin expression by binding to its promoter. Consequently, ESRRA abrogation decreased the secretion of leptin from both visceral adipocytes and BMAds, promoting

BMSCs to differentiate into osteoblasts rather than adipocytes.

Moreover, pharmacological inhibition of ESRRA significantly restricted marrow adipose tissue expansion and promoted bone formation in an adipocyte-rich bone milieu of obese mice, thereby preventing bone loss and high marrow adiposity.

This study provides a new method for treating bone disorders especially in clinical conditions associated with high marrow adiposity by targeting ESRRA.

More information: Tongling Huang et al, Targeting adipocyte ESRRA promotes osteogenesis and vascular formation in adipocyte-rich bone marrow, *Nature Communications* (2024). DOI: 10.1038/s41467-024-48255-8

Provided by Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences