BEB
Conference on Biomedical Engineering and Biotechnology

Paper No.

Treatment with soluble bone morphogenetic protein type 1A receptor fusion protein alleviates irradiation-induced bone loss in mice through increased bone formation and reduced bone resorption

Shen Wang

Peking University

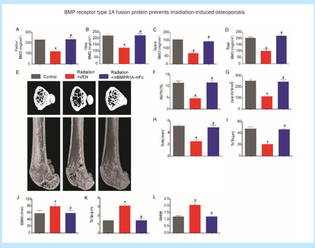
Introduction

An increased fracture risk is often observed in cancer patients undergoing radiotherapy (RT), particularly at sites within the field of radiation. Therefore, the development of appropriate therapeutic options to prevent RT-induced bone loss is urgently needed. A soluble form of the BMP receptor type 1A fusion protein (mBMPR1A-mFc) serves as an antagonist to endogenous BMPR1A. Previous studies have shown that mBMPR1A-mFc treatment increases bone mass in both ovary-intact and ovariectomized via promoting osteoblastic bone formation and inhibiting osteoclastic bone resorption. The present study was designed to investigate whether mBMPR1A-mFc administration prevents radiation-induced bone deterioration in mice. .

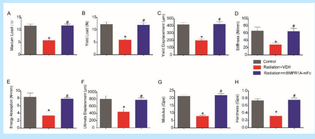
Methods

- **We constructed an animal model of radiation-induced osteoporosis by exposure to a 2-Gy dose of X-rays..**
- **Micro-CT, histomorphometric, bone-turnover, and mechanical analyses were used to prove the effect of mBMPR1A-mFc on trabecular microarchitecture deterioration after RT**

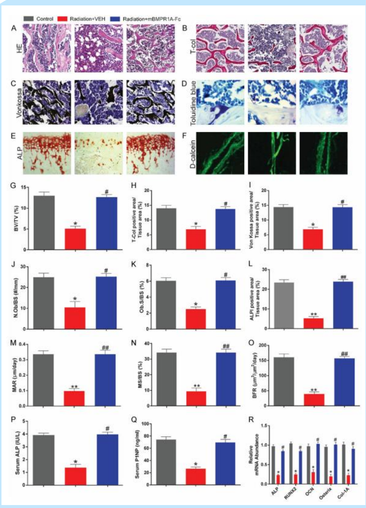
Results



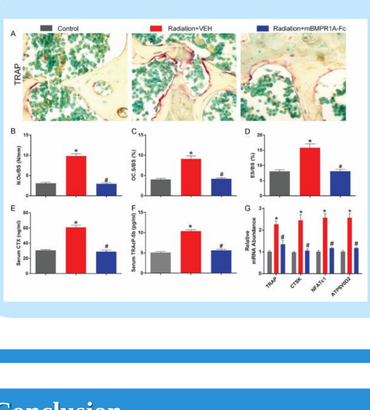
Following RT, the aBMD values of the whole body (Figure 1D), lumbar spine (Figure 1C), distal femoral metaphysis (Figure 1A), and proximal tibial metaphysis (Figure 1B) were obviously reduced. As expected, treatment with mBMPR1A-Fc almost completely prevented the negative effects of RT on bone density (Figure 1A-D).



The femoral biomechanical structural properties were measured in the three-point bending test (Figure 2A-F). The femoral biomechanical material properties were examined in the nanoindentation test (Figure 2G, ,2H).



Representative static histomorphometric images for each group obtained by HE, total collagen, toluidine blue, von Kossa, and ALP staining are shown in (Figure 3A-E). RT led to an obvious decrease in the trabecular bone in the femur compared with that of the control group, which was characterized by a significant reduction in the BV/TV (Figure 3G), total collagen positive areas/tissue area (Figure 3H), von Kossa positive area/tissue area (Figure 3I), ALP-positive areas/tissue area (Figure 3L), N.Ob/BS (Figure 3J), and Ob.S/BS (Figure 3K) compared with these parameters in the control group. RT led to an obvious decrease in the trabecular bone in the femur compared with that of the control group, which was characterized by a significant reduction in the BV/TV (Figure 3G), total collagen positive areas/tissue area (Figure 3H), von Kossa positive area/tissue area (Figure 3I), ALP-positive areas/tissue area (Figure 3L), N.Ob/BS (Figure 3J), and Ob.S/BS (Figure 3K) compared with these parameters in the control group. Additionally, significant decreases in serum ALP and P1NP levels were observed in the RT-VEH group compared with those of the control group. After mBMPR1A-Fc treatment, serum ALP and P1NP in the RT-mBMPR1A-Fc group were significantly higher than those in the RT-VEH group (Figure 3P, ,3Q).3Q). Furthermore, the mRNA levels of ALP, Runx2, OCN, Osterix, and Col-1A were assessed by RT-PCR (Figure 3R).



Representative TRAP staining of femurs is shown in Figure5A. A histomorphometric analysis revealed a significant increase in the N.Oc/BS (Figure 5B), Oc.S/BS (Figure 5C), and ES/BS (Figure 5D) in the RT-VEH group compared with that of the control mice. Consistent with the increased osteoclast numbers in the RT-VEH group, serum CTX-1 (Figure 5E) and TRAP5b (Figure 5F) levels were also increased, reflecting increased osteoclastic bone resorption after RT. Additionally, the RT-PCR results revealed that genes related to osteoclastogenesis, such as TRAP, CTSK, NFATc1, and ATP6V0D2, were all significantly increased after RT (Figure 5G).

Conclusion

In conclusion, our study indicated that mBMPR1A-mFc administration could alleviate radiation-induced osteoporosis in mice, as evidenced by serum biochemical, biomechanical, micro-CT, and histological analyses. The bone-protective effects of mBMPR1A-mFc might be attributed to a combination of promoting bone formation and suppressing bone resorption. Moreover, several signaling pathways may be involved in the underlying mechanisms, including the Wnt3a/Lrp5/β-catenin and RANKL/RANK/OPG pathways. This observation suggests that mBMPR1A-mFc is a safe and effective dual-action therapeutic agent that may be effective against radiation-induced bone loss by promoting bone formation while inhibiting resorption.