INTRODUCTION:

Sclerostin is a negative regulator of bone formation and treatment with a sclerostin monoclonal antibody (Scl-Ab) results in increased bone formation and bone mass in animal models. Previous studies demonstrated that Scl-Ab significantly increased bone mass and bone strength at the site of fracture in a closed fracture model in rats (1-2). However, the effect of Scl-Ab on healing of open fracture has not yet been reported in rats. The objective of this study was to investigate the effects of systemic administration of Scl-Ab on fracture repair in an open fracture model in rat femur. Further, we assess the effects of Scl-Ab on angiogenesis of the fracture site in this rat model.

METHODS:

Total 60 six-month-old male SD rats were used in this study. The rats were randomly divided into Scl-Ab group and vehicle group after a transverse osteotomy performed at the mid-shaft of the right femur. One day post-surgery, rats were treated with Scl-Ab (s.c. injection, 25 mg/kg, 2 times per week) or vehicle for 3 or 6 weeks. After sacrifice, callus samples were collected and subjected to the following analyses: micro-CT-based angiography for the total vessel volume, the average vessel diameter and the vessel volume fraction, microCT for callus volume fraction and BMD, four-point mechanical testing for ultimate load, energy to failure and stiffness, as well as histology. All the evaluation followed our established protocols (3-5).

RESULTS:

Micro-CT based angiography demonstrated more vessel-like structures in Scl-Ab group compared to the vehicle group at 3 weeks (Figure 1). Micro-CT evaluations showed Scl-Ab groups had significantly higher callus volume fraction and BMD in both 3 and 6 weeks post-fracture compared to vehicle groups (Figure 2). H&E staining showed more granulation tissues at 3 weeks and more bony tissue at 6 weeks in the Scl-Ab treated calluses than vehicle-calluses. Four-point bending testing also showed significantly higher ultimate load (+98%) in Scl-Ab group than vehicle group and the stiffness and energy to failure were also tended higher in Scl-Ab group at 6 weeks post fracture (Figure 3).

DISCUSSION:

This study demonstrated that Scl-Ab enhanced bone healing in an osteotomy rat model, with increased bone formation, bone mass and bone strength at the fracture site. Fracture repair is complex, involving a coordinated sequence of biological processes that includes angiogenesis. Consistent with the enhancement of bone healing with Scl-Ab, it appeared that callus vascularization was increased in the Scl-Ab group at the 3-week time point. Collectively, our results support the potential of systemic Scl-Ab administration to enhance open fracture healing in patients. Quantification for ratio of cartilage area and bone area to total callus area and rate of bone remodeling will be conducted in future.

SIGNIFICANCE:

This study demonstrated that Scl-Ab enhanced bone healing in an osteotomy rat model, supporting the potential of systemic Scl-Ab administration to enhance open fracture healing in patients.

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REFERENCES: