Hematopoietic Cells Regulate Fracture Healing in Neurofibromatosis

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INTRODUCTION:

Recent data shows that macrophage cells are critical for bone fracture healing. In addition, this cell type regulates the pace of fracture repair. Neurofibromatosis is associated with a slowed pace of fracture repair and inhibitedrosteogenesis, and this contributes to conditions such as tibial pseudoarthrosis. Here we determined the contribution of hematopoietic cells in fracture repair in NF1.

METHODS:

Mice in which the Nf1 gene is conditionally deleted by injection of an adenovirus expressing cre recombinase (Nf1f/f) were used for the study. Tibia fractures were generated and fixed with an intramedullary pin. The quality of the repair was assessed 21 days after fracture using micro-CT and histomorphometry. Bone marrow transplantations were performed on these animals using donor bone marrow from Nf1f/f or wild type mice of the same background. All of the mice were of the same age, and half were male and half female in each cohort. All were treated with an adenovirus. 12 mice were examined in each group: recipient Nf1f/f mice with wild type donor; recipient Nf1f/f mice with Nf1f/f donor; Nf1f/f mice without a bone marrow transplantation; and wild type mice without a transplantation.

RESULTS:

Nf1f/f mice without a bone marrow transplantation had a 27% lower bone density at the tibia fracture site and a 35% increase in the proportion of fibrous tissue (both $p<0.01$ by t-test). Recipient Nf1f/f mice with Nf1f/f donor marrow showed a bone density at the fracture site and a proportion of fibrous tissue at the fracture site the same as for control Nf1f/f mice. Recipient Nf1f/f mice with wild type donor marrow had a 19% increase in bone density and a 29% decrease in the percent of fibrous tissue at the fracture site (both $p<0.01$ by t-test). There were no mesenchymal or bone cells found in the recipient animals from the donor animals, showing that the effect is from the hematopoietic cell population.

DISCUSSION AND CONCLUSION:

This data shows that hematopoietic cells regulate the quality of fracture repair in NF1 in mice. A role for hematopoietic cells was previously demonstrated in other conditions, such as in aging, and this data extends the notion that these cell types orchestrate bone repair to a genetic condition influencing bone repair.

Taken together, this suggests that an approach to target hematopoietic cells, such as macrophage cells, could be developed into a therapy to improve bone healing in neurofibromatosis. Pharmacologic and cell therapy approached are being investigated to achieve this goal.

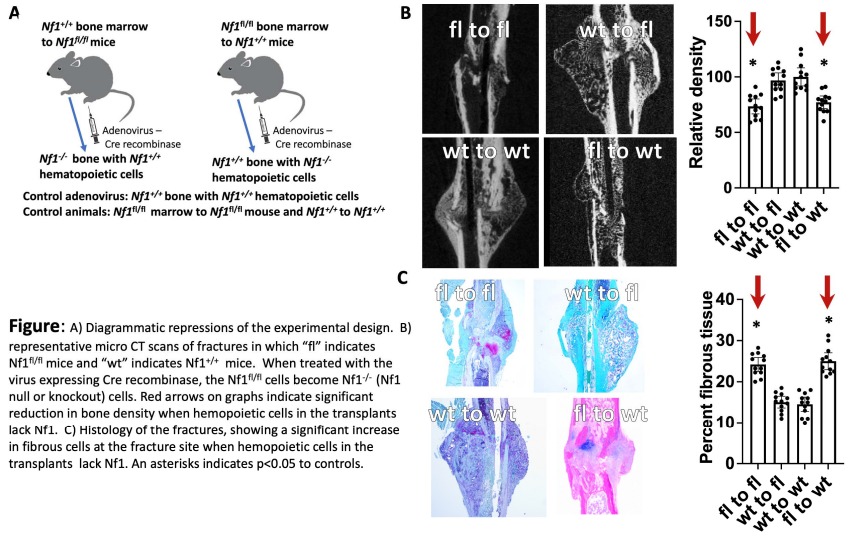

Figure: A) Diagrammatic repressions of the experimental design. B) representative micro CT scans of fractures in which "fl" indicates $Nf1^{fl/fl}$ mice and "wt" indicates $Nf1^{+/+}$ mice. When treated with the virus expressing Cre recombinase, the $Nf1^{fl/fl}$ cells become $Nf1^{-/-}$ (Nf1 null or knockout) cells. Red arrows on graphs indicate significant reduction in bone density when hemopoietic cells in the transplants lack Nf1. C) Histology of the fractures, showing a significant increase in fibrous cells at the fracture site when hemopoietic cells in the transplants lack Nf1. An asterisks indicates $p<0.05$ to controls.