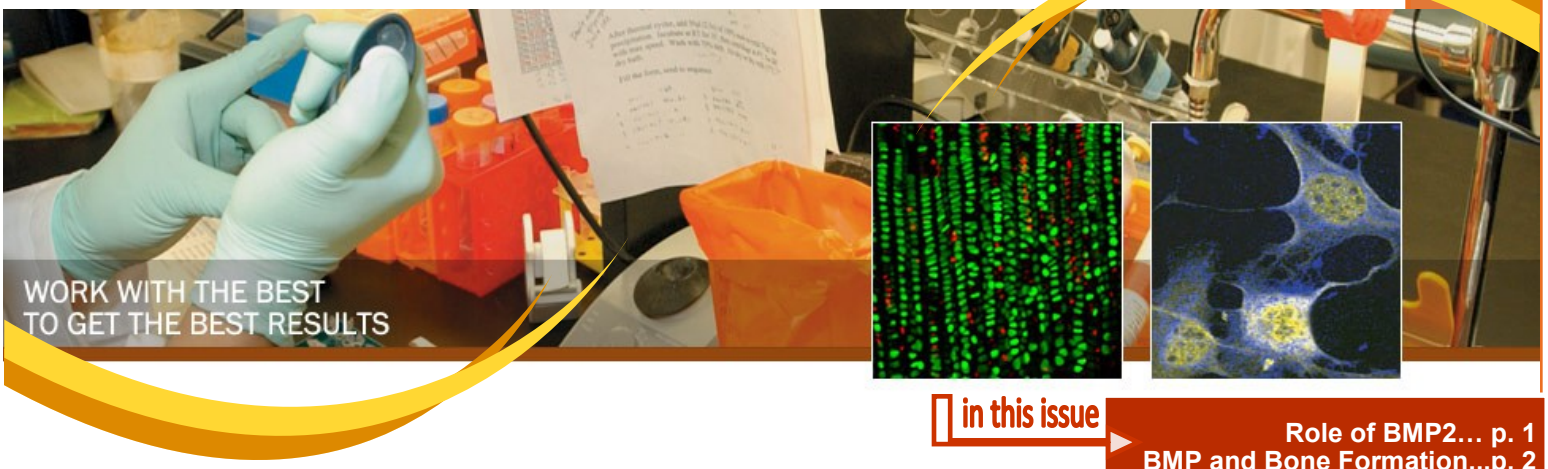
MUSCULOSKELETAL RESEARCH CENTER at Washington University

Musculoskeletal Research Center

Vol 4|Issue 7|Mar 2013



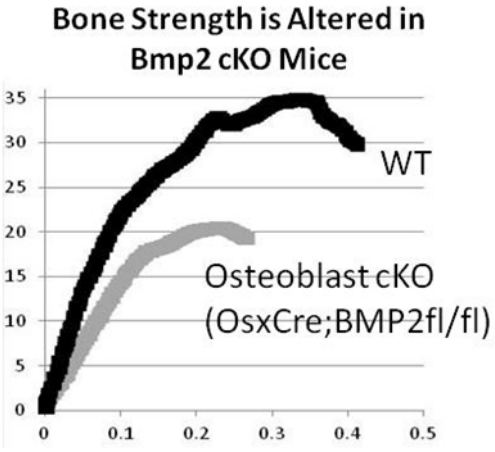
in this issue

Dr. Vicki Rosen, our Symposium Speaker on March 21, is a pioneer in the field of Bone Morphogenetic Proteins (BMPs). This issue of the MRC Newsletter will highlight some of the BMP work being done at Washington University.

The Role of BMP2 in Stress Fracture Healing and Bone Strength

JA McKenzie, SH McBride, MJ Silva

BMP2 is expressed by vascular endothelial cells and osteoblasts. We have observed expression in these cells, along with upregulation of mRNA, soon after creation of a stress fracture. While BMP2 is required for endochondral bone healing after full fracture, it is not clear if it is required for intramembranous bone formation, which is predominant in stress fracture healing. Using *Bmp2*-floxed mice (V. Rosen) we have created conditional knockout (cKO) of *Bmp2* in endothelial cells (VECad-Cre) and in osteoblasts (Osx-Cre). Stress fracture healing is normal in endothelial cKO mice. By contrast, osteoblast cKO of *Bmp2* results in osteopenia and impaired bone strength (at 12 and 24 weeks). The decrease in bone strength is due mainly to smaller bone size. Ongoing studies are assessing stress fracture healing in osteoblast cKO mice as well as the basis for the material defect.



Avioli Musculoskeletal Seminar Series

BJCIH Bldg. | 11th floor
A/B Conference Room
Fridays @ 9am

3/8	Maurizio Pacifici, PhD *Children's Hospital of Philadelphia*
3/15	Daniel Lucas-Alscaraz, PhD *Albert Einstein College of Med.*
3/22	No Seminar
3/29	No Seminar
4/5	Clarissa Craft, PhD *Cell Biology & Physiology*
4/12	Yousef Abu-Amer, PhD *Orthopaedic Surgery*
4/19	Gabriel Mbalaviele, PhD *Bone & Mineral Diseases*
4/26	Sara McBride, MD *Silva Lab*
5/3	Debabrata Patra, PhD *Orthopaedic Surgery*

For more information about the MRC and the Cores, please click here:
http://muscoloskeletalcore.wustl.edu

Please remember to include reference to support from the Musculoskeletal Research Center in your abstracts and publications.
Cite Grant # P30AR057235
from the National Institute Of Arthritis And Musculoskeletal And Skin Diseases.

BMP and Negative Regulation of Bone Formation

J. Lim, F Long

The bone morphogenetic proteins were originally identified for their remarkable ability to induce new bone formation. Recently, mouse genetic studies have shown that BMP signaling is essential for the formation of skeletal elements during mouse embryonic development. However, the role of BMP signaling during postnatal bone formation remains poorly understood. To address this question, we used an inducible mouse model system to conditionally delete Alk3 (Bmpr1a) in osteoblast-lineage cells. Unexpectedly, conditional deletion of Alk3 in osteoblast-lineage cells resulted in a dramatic increase in bone mass that affected the majority of skeletal elements, including the long bones and the skull (Figure 1). Histomorphometric analyses revealed that the high bone mass phenotype in Alk3 conditional knockout mice was caused by an increase in osteoblast numbers and function but not due to osteoclast defects. Taken together, these results suggest that BMP signaling through Alk3 in osteoblast-lineage cells inhibits postnatal bone formation in the mouse. Ongoing experiments are designed to elucidate the molecular mechanism underlying the unexpected negative regulation of bone formation by Alk3 signaling.

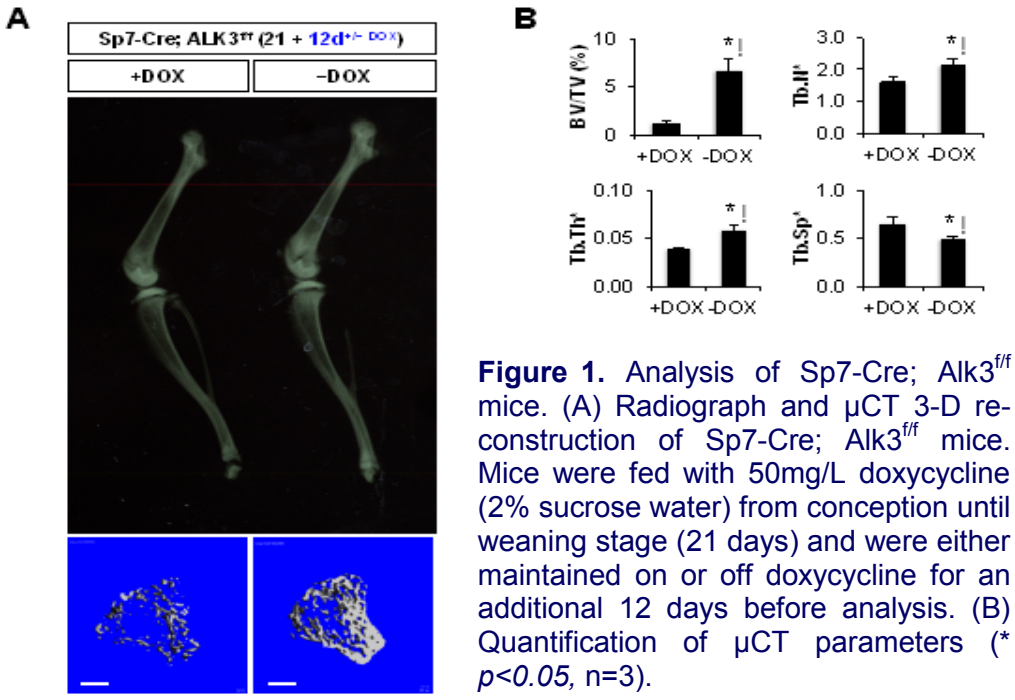


Figure 1. Analysis of Sp7-Cre; $Alk3^{f/f}$ mice. (A) Radiograph and μCT 3-D reconstruction of Sp7-Cre; $Alk3^{f/f}$ mice. Mice were fed with 50mg/L doxycycline (2% sucrose water) from conception until weaning stage (21 days) and were either maintained on or off doxycycline for an additional 12 days before analysis. (B) Quantification of μCT parameters (* *p<0.05,* n=3).

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Animal Model Highlight

David Beebe: BMP Mouse Models Available at Washington University

Bmpr1a flox – since Bmpr1a is typically the most abundant type I BMP receptor in most tissues, conditional deletion of this gene often reveals important aspects of BMP signaling. Deletions that remove all BMP receptors in a tissue are more informative than removal of Smad4, for instance, since BMP receptors can signal by Smad-dependent or Smad-independent pathways.

Bmpr1b germline KO – since this type I BMP receptor can be redundant with Bmpr1a, double KOs are often needed to reveal BMP function.

Acvr1 flox – the third type I BMP receptor. Also frequently found in tissues with Bmpr1a, where the receptors can function in a redundant manner.

Bmp4 flox – Useful in systems in which Bmp4 is the critical BMP.

Bmp7 flox – Useful in systems in which Bmp7 is the critical BMP.

Tgfbr2 flox – effective for determining whether TGF-beta signaling is important. Since there is only one type II TGF-beta receptor, deletion of both alleles should eliminate all TGF-beta signaling.

Bmp-Smad reporter mice (in collaboration with Ken Cho's lab at UC Irvine) – a sensitive reporter strain making use of a Smad-response element fused to the beta-galactosidase gene to localize canonical BMP signaling. To date, we have only used embryos supplied by Dr. Cho's group.

Smad4 flox – useful for determining whether canonical Smad signaling (BMP, TGFbeta, activin, etc.) is functioning in your system.

Smad1, 5 flox - Double conditional KOs useful for determining if Smad-dependent BMP signaling is important in your system of interest. (Note: Smad8/9 may function in some BMP pathways)

Musculoskeletal Research Center

3rd Annual Winter Symposium

March 21, 2012 | 1-5pm
Eric P. Newman Educational Center

Featured Speaker:

Dr. Vicki Rosen

Harvard School of Dental Medicine

If you have any questions regarding the MRC, please contact:

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