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RESEARCH GOALS: The primary goal of our research is to study the role of bone mesenchymal stem cells in bone development and remodeling.

RESEARCH SUMMARY AND SIGNIFICANCE: Bone marrow mesenchymal stem cells have the potential to differentiate to lineages of mesenchymal tissues, including osteoblasts, adipocytes, chondrocytes, fibroblasts and myoblasts. We are studying the microenvironment that is necessary for differentiation of the multipotential stem cells into functionally distinct cell types such as osteoblasts.

Parathyroid hormone and TGF- β 1 are the important factors that regulate differentiation of mesenchymal cells into osteoblasts. Using a genetic approach, we found that the TGF- β type II receptor (T β RII), a serine/threonine kinase, forms an endocytic complex with PTH1R in response to PTH and regulates both PTH and TGF- β signaling. T β RII directly phosphorylates the cytoplasmic domain of PTH type I receptor to induce endocytosis of the PTH1R/T β RII complex. Conditional disruption of T β RII in osteoblasts results in a skeletal phenotype similar to that seen in mice expressing a constitutive active PTH receptor; namely increased trabecular bone with reduced cortical bone. These studies reveal a previously unrecognized function for T β RII and a mechanism for integration of PTH and local growth factor at level of membrane receptor for differentiation of MSCs.

CURRENT PROJECTS:

1. Mechanism of coupling bone resorption and formation
2. PTH-induced endocytosis to integrate bone remodeling signals
3. The role of Smad1 in osteoblast differentiation

RECENT PUBLICATIONS (Past 3 years):

1. Shi W, Chang C, Nie S, Xie S, Wan M, **Cao X**: Endofin acts as a Smad anchor for receptor activation in BMP signaling. *Journal of Cell Science*. 2007; 120 (7): 1216-1244. This paper has been featured on the Front Cover with two commentaries: "High Five in BMP Signaling" and "Endo-fin-ally a SARA for BMP receptors" in the same issue of JCS. PMID: 17356069.
2. Qiu T, Oelschlager D, Shen X, Grizzle W, **Cao X**: Control of prostate cell growth: BMP antagonizes androgen mitogenic activity with incorporation of MAPK signals in Smad1. *EMBO J*. 2007; 26(2): 346-57 PMID: 17183365.
3. Li P, Oparil S, Novak L, **Cao X**, Shi W, Lucas JA, Chen YF: ANP Signaling Inhibits TGF β -Induced Smad2 and Smad3 Nuclear Translocation and Extracellular Matrix Expression in Rat Pulmonary Arterial Smooth Muscle Cells. *J Appl Physiol*. 2007; 102(1):390-398. PMID: 17038494

4. Ma H, Lu Z, Sun Y, Peng T, Shuai Z, Ma Y, Zhang Y, Wang L, **Cao X**, Wang H: Selection of Donor Nuclei in Somatic Cell-mediated Gene Transfer Using a Co-transfection Method. *J Reprod Dev.*2007; 53(1):95-104. PMID: 17077582
5. Huang J., Lu C., Liu X., **Cao X.** and Wan M. Jab1 Mediates Protein Degradation of Rad9/Rad1/Hus1 Checkpoint Complex. *J Mol Biol.* 2007 10;371(2):514-27
6. X Wu, W Shi and **X Cao.** Multiplicity of BMP signaling in skeletal development. *Ann NY Acad Sci.* 2007;1116:29-49. PMID: 18083919
7. Tang Y, Liu Z, Zhao L, Clemens T, **Cao X:** Smad7 directs β -catenin to cell membrane E-cadherin complexes for promotion of cell-cell adhesion. *J. Biol. Chem.* (2008)283:23956-23963. This paper has been evaluated as the most interesting paper published in the biological sciences in Faculty of 1000 Biology. PMID: [18593713](#)
8. Lu W, Kim K, Feng X, **Cao X** and Li Y: R-spondin1 Acts through LRP6 to Synergize Strongly with Wnt3A in Inducing Mesenchymal C2C12 Osteoblastic Differentiation and Osteoprotegrin Expression. *FEBS Lett.* 2008 ; 5;582(5):643-50.
9. Li P, Wang D, Lucas J, Oparil S, Xing D, **Cao X**, Lea Novak L, Renfrow M, Chen YF: Atrial Natriuretic Peptide Inhibits Transforming growth factor β -Induced Smad Signaling and Myofibroblast Transformation in Mouse Cardiac Fibroblasts. *Circulation Research.* 2008 1;102(2):185-92
10. Wan M, Yang C, Yuan H, Wu X, He X, Lu C, Chang C, **Cao X.** Parathyroid Hormone Activates β -catenin Signaling through LRP5/6. *Gene & Development.* 2008 22(21):2968-79
11. Allyson K McDonough, MD, Richard S Rosenthal, MD, **Xu Cao**, Ph.D, Kenneth G Saag, MD, MSc. The Effect of Thiazolidinediones on Bone Mineral Density and Osteoporosis. *Nature Clinical Endocrinology and Metabolism.* 2008 (9): 507-13. PMID: 18695700
12. Zhang F, Shi W, Qiu T, Wu X, Wan C, Wang Y, Wan M, Clemens TL and **Cao X.** Sustained BMP Signaling in Osteoblasts Stimulates Bone Formation by Promoting Angiogenesis and osteoblast differentiation. *J Bone Miner Res.* 2009 24(7):1224-33.
13. Tang Y, Wu X, Lei W, Pang L, Wan C, Shi Z, Nagy T, Feng X, Peng X, Hu J, Wim Van Hul, Zhao L, Wan M, and **Cao X:** TGF β 1 Induces Migration of Bone Mesenchymal Stem cells to Couple Bone Resorption and Formation. *Nature Medicine.* 2009 15(7):757-65. This research article is highlighted with a commentary in the same issue of Nature Medicine. It is also evaluated as the most interesting paper published in the biological sciences in Faculty of 1000 Biology.