Bone as an Endocrine Organ: UAB Researchers Seek Answers to Questions about the Relationship between Bone Health and Diabetes

UAB obesity and osteoporosis researchers are joining forces to explore the possible intersection of bone health and diabetes using the UAB Osteoporosis Prevention and Treatment Clinic as their lab. Barbara Gower, PhD, (Director, Core Laboratory of the DRTC, NORC, and CCTS), Sarah Morgan, MD, RD (Director, UAB Osteoporosis Prevention and Treatment Clinic) and Beth Kitchin, PhD, RD (UAB Nutrition Sciences and Patient Educator, UAB Osteoporosis Clinic) are working together to evaluate the effects of altered bone metabolism and the subsequent effects on glucose metabolism. Thinking about bone as an endocrine organ is a novel approach to the treatment of diabetes and metabolic syndrome.

The hypothetical connection between bone and glucose metabolism is a new and exciting area with potential for innovative research, new discoveries and improved patient care and outcomes. The link between the two seems to be the bone protein osteocalcin (OC). In mice, this effect is specific to the under-carboxylated form (ucOC). Whether this is true in humans is not clear. Most human studies have been cross-sectional and have used poor measures of insulin sensitivity. The UAB researchers plan to conduct a clinical intervention with UAB Osteoporosis clinic patients. Treatment with anabolic and anti-resorptive drugs will be used as a tool to alter endogenous production of total and undercarboxylated OC. The investigators will determine if changes in either form of OC are associated with changes in insulin sensitivity and beta-cell function.
Select Recent Publications by CMBD Members

Dr. Selvarangan Ponnazhagan's lab recently published an article in the *Journal of Biological Chemistry* (Sawant A, et al.) which identified for the first time that Noggin, a protein known so far to have antagonistic effect on BMP signaling on osteogenesis by binding to the BMP ligand, also induces adipocyte differentiation of mesenchymal stem cells (MSC) independently of the three major known adipocyte differentiation pathways. The evidence for this was identified in normal and obese mice as well as increased plasma noggin levels as surrogate in human patients with obesity.

Dr. Yi-Ping Li has had an article accepted into the *Journal of Bone and Mineral Research* (Yang DQ, et al.) in which his lab determined that ATP6ap1 (Ac45), an accessory subunit of the V-ATPase complex, is important for both osteoclast differentiation and function. It further demonstrates the essential role of Ac45 in osteoclast-mediated extracellular acidification and protease exocytosis, as well as the ability of Ac45 to guide lysosomal intracellular trafficking to the ruffled border, potentially through its interaction with the small GTPase Rab7. Overall, their work indicates that Ac45, a type I transmembrane protein, may be an ideal therapeutic target for osteolytic diseases such as osteoporosis and rheumatoid arthritis.

Dr. Xu Feng published a manuscript in the *Journal of Interferon and Cytokines* (Cheng J, et al.). While it had been well know that interferon gamma (IFN-?) exerts biphasic effects on osteoclastogenesis, the underlying mechanism remained incompletely understood. In this recent work, Dr. Feng's group further investigates the molecular mechanism by which IFN-? regulates osteoclastogenesis, leading to a better understanding of the mechanism of IFN-?-mediated osteoclastogenesis.

Dr. Xu Feng has also recently published in *J Bio Chem* (Jules J, et al.). Interleukin-1 (IL-1)-mediated osteoclastogenesis requires permissive levels of RANKL or RANKL pretreatment. However, the molecular
mechanism by which IL-1-mediated osteoclastogenesis requires RANKL is not fully understood. This paper reports their new finding that RANKL is involved in IL-1-mediated osteoclastogenesis by rendering osteoclast and NFATc1 genes responsive to interleukin-1. This represents a novel mechanism of IL-1-mediated osteoclastogenesis.

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