FUNCTIONAL MEDICINE UPDATE
JANUARY 2009
ISSN 1092-1761
Vol. 29, No. 1

Connective Tissue and Extracellular Matrix Physiology

As preparation for his discussion with Dr. Helene Langevin this month, Dr. Bland discusses her 2006 article titled "Connective Tissue: A Body-Wide Signaling Network" which was published in *Medical Hypotheses*. This article focuses on the hypothesis that connective tissue functions as a body-wide mechanosensitive signaling network. Dr. Langevin writes, "Since connective tissue is intimately associated with all other tissues (e.g. lung, intestine), connective tissue signaling may coherently influence (and be influenced by) the normal or pathological function of a wide variety of organ systems. Demonstrating the existence of a connective signaling network therefore may profoundly influence out understanding of health and disease." REF #1

Bone as a Dynamic Organ

As a corollary to his introduction on connective tissue, Dr. Bland discusses the subject of osteoporosis. Bone undergoes significant turnover as compared to other organs in the body. A review by British researchers was published in the *Journal of Clinical Pathology* in 2008 that details how complex intercellular signaling between osteoprogenitor cells and mature osteoblasts, osteocytes and osteoclasts regulates and balances activities of bone cells during remodeling and growth. REF #2-3

Dr. Bland revisits an article by researchers from Columbia University that was published in *Cell* in 2007. This group suggested that the regulation of bone remodeling by an adipocyte-derived hormone may exert a feedback control of energy homeostasis. To test this hypothesis, they looked (in a mouse model) for genes expressed in osteoblasts, encoding signaling molecules and affecting energy metabolism. Dr. Bland goes on to highlight a review paper authored in 2008 by Dr. George Wolf of the University of California, Berkeley. In this paper published in *Nutrition Reviews*, Dr. Wolf describes how both osteoclasts (the cells responsible for bone resorption) and osteoblasts (the cells responsible for bone formation) are under multi-hormone control. REF #4-5

Where will the research take us? Dr. Bland discusses an article published in *Nature* in 2008 titled "New Role of Bone Morphogenic Protein 7 in Brown Adipogenesis and Energy Expenditure." Factors that specify the developmental fate and function of white and brown adipose tissue are poorly understood. In this study, a collaborative group of researchers demonstrate that whereas some members of the family of bone morphogenic proteins (BMPs) support white adipocyte differentiation, BMP7 singularly promotes differentiation of brown preadipocytes even in the absence of the normally required hormonal induction cocktail. The data from this study reveal an important role of BMP7 in promoting brown adipocyte differentiation and thermogenesis *in vivo* and *in vitro*, and provide a potential new therapeutic approach for the treatment of obesity. REF #6

The Wnt Signaling Pathway and its Role in Bone Remodeling and Repair

The Wnt genes encode a highly conserved class of signaling factors required for the development of several types of tissues, including musculoskeletal and neural structures. Dr. Bland describes the Wnt signaling pathway and discusses the increasing evidence that that Wnt signaling is critical for bone mass accrual, bone remodeling, and fracture repair. REF #7

One of the most intensively studied regulators of bone remodeling is LDL-receptor related protein 5 (Lrp5). Loss- and gain-of-function mutations in this broadly expressed gene affect bone formation, causing osteoporosis and high bone mass, respectively. Dr. Bland discusses what he considers to be a breakthrough article that appeared in *Cell* in November 2008. Although Lrp5 is viewed as a Wnt coreceptor, the authors of this study show that Lrp5 inhibits expression of the rate-limiting biosynthetic enzyme for serotonin in enterochromaffin cells of the duodenum. By identifying duodenum-derived serotonin as a hormone inhibiting bone formation in an Lrp5-dependent manner, these researchers feel the study broadens the understandin of bone remodeling and suggests potential therapies to increase bone mass. An editorial titled "When the Gut Talks to Bone" appears in the same issue of Cell and provides further insight into the findings of the study. REF #8-9

Dr Bland closes this discussion by mentioning additional relevant articles, including another recent study on serotonin secretion—this one by Yale reseachers—titled "IL1-beta and LPS-induced Serotonin Secretion is Increased in EC Cells Derived from Crohn's Disease." REF #10-11

Clinician/Researcher of the Month

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Dr. Helene Langevin is a Research Associate Professor in the Department of Neurology at the University of Vermont. She received her MD from McGill University in 1978 and completed her residency in internal medicine at Johns Hopkins Hospital, where she was an Endocrinology and Metabolism Fellow. Dr. Langevin is also a licensed acupuncturist and has served as past co-president of the Society for Acupuncture Research.

The research interests of Dr. Langevin's laboratory are the mechanism of action of acupuncture and the interaction between connective tissue and sensory nervous system. She and her colleagues are currently investigating the hypothesis that transduction of a mechanical signal (created by needle/tissue coupling and further movements of the needle) to a cellular response underlies some of the therapeutic effects of acupuncture.

Dr. Langevin's long-term goal is to understand how the effect of mechanical forces on connective tissue matrix composition may influence sensory afferent input originating from that connective tissue. Understanding these interactions may provide important insights into the pathogenesis of musculoskeletal pain.

Dr. Bland and Dr. Langevin have a detailed conversation about her research pursuits. They specifically refer to and discuss many of the publications Dr. Langevin and her colleagues have published over the last decade. REF #12-15

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