Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

Wnt Inhibition Decreases Trabecular Bone in a Mouse Model of Fibrous Dysplasia

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Background: G protein-coupled receptor (GPCR) signaling mediates a wide spectrum of physiological functions, including bone development and remodeling. Fibrous dysplasia (FD) is a common skeletal dysplasia where normal bone and bone marrow are replaced by fibrous tissue and expansile trabecular bone lesions. The craniofacial bones are often involved, leading to pain and facial deformities. FD is a mosaic disease caused by a somatic mutation in the *GNAS* gene encoding the G-protein alpha subunit (Gsα) that leads to constitutive activation of the G_s signaling pathway. Unfortunately, FD has no effective medical treatments.

Major challenges have hampered the development of pharmacologic strategies that specifically target *GNAS* or the $G_s\alpha$ protein. We previously developed the Col1(2.3)/Rs1 mouse model (Rs1) in which the G_s signaling pathway is activated specifically in bone by an engineered GPCR protein. These mice showed increased trabecular bone formation with loss of marrow space and cortical bone, which strongly resembles human FD (1–4). There was also a dramatic increase in the number of immature osteoblasts present in the FD lesions, suggesting that activation of G_s signaling caused an accumulation of these cells. Our prior studies showed increased Wnt signaling, which may be a major driver of this effect. Furthermore, blocking the G_s signaling could reverse the bone phenotype, providing proof-of-concept for finding drugs that could reverse the phenotype. Therefore, we administered the Wnt inhibitor LGK974, currently used in human clinical trials, to the Rs1 mice to test if the FD lesions could be pharmacologically reversed.

Methods: We administered LGK974 in 4-week-old Rs1 and non-Rs1 mice. We used a low dose (5mg/kg) for 8 weeks or high dose (30mg/kg) for 4 weeks. The mice were evaluated by histology and micro computed tomography (micro-CT) for mineral density (mg/cm^3), bone volume (mm^3), and trabecular thickness (um).

Results: LGK974 decreased β-catenin levels in bone on western blots. In the low-dose group, the histology and micro-CT showed no statistically significant differences between drug and control groups. In the high-dose group, the micro-CT showed significantly decreased trabecular bone thickness (p=0.0364, n=3) in the drug-treated group (22±2μm) compared with controls (17±2μm). Furthermore, histology showed resorption of the abnormal bone; however, the fibrocellular infiltrate in the Rs1 mice was still present.

Conclusions: Wnt inhibition can lead to decreased fibrous dysplastic bone, but separates abnormal bone formation from the fibrocellular infiltrate. These results provide new insight into understanding interactions between the Wnt and G_s signaling pathways in FD pathogenesis and bone formation.

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Neuroendocrinology and Pituitary

CASE REPORTS IN SECRETORY PITUITARY PATHOLOGIES, THEIR TREATMENTS AND OUTCOMES

The Ever Confusing Cushing's Work Up: Is It Real? Is It Pseudo Cushing's'? Or Could It Be Factitious

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The Ever Confusing Cushing's Work Up: Is it real? Is it pseudo Cushing's, or could it be factitious?

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Case Presentation:

A 50 year old female initially presented with progressive weight gain and mood swings. She had normal 24 h urine cortisol, but an elevated midnight serum cortisol. She underwent transphenoidal surgery for a presumed ACTH-dependent Cushing's disease. Pathology was not supportive of a pituitary adenoma, showing adenohypophyseal tissue with focal expansion of the acini. The surgery was complicated by hypothyroidism and growth hormone deficiency. She was able to weaned off of the steroids after a few months. She had recurrence of her initial symptoms, she was found to have elevated late evening and morning cortisol levels. She underwent a bilateral adrenelactomy for "recurrence of the cyclical Cushing's symptoms." She was started on HC replacement; 10 mg AM and 2.5 mg PM, florinef 0.05 mg daily. She slowly lowered the hydrocortisone dose, and as a result lost 120 lbs.

Three years later she presented with fatigued and gaining weight, by that time she was on Hydrocortisone 3.75 mg AM, 1.25 mg evening, and fludrocortisone 0.1 mg/day. ACTH was 355 (6–48 pg/ml), serum cortisol 10 (8–19 ug/dl) on Hydrocortisone and < 1.0 ug/dl off cortisone. The 24 h urine free cortisol < 1.0 (10–24 ug/34h), and 17 OH-corticosteroids < 4.8(4–14 mg/dl). A possible adrenal remnant was seen on abdominal CT, surgically removed of the lesion showed a lipoma.

She was referred to Neurosurgery for a second pituitary surgery for the concern Cushing's recurrence. A pituitary MRI revealed a small potential microadenoma. The small dose of hydrocortisone was held for 48 h and an 8 AM test dose: Serum cortisol < 1.20 mcg/dl (3–18), ACTH 1,077 pg/ml (5–72), 24 h urine cortisol < 1.5 mcg/24h (3.5–45), 24 h urine cortisone 10 mcg/24h (17–129), and two midnight salivary cortisol were 128 and 265 ng/dl (< 100 ng/dl). There was a concern raised by the laboratory for a contaminated salivary sample, as the salivary cortisol to cortisone ratio was concerning for contamination with exogenous steroid (1)

Discussion:

Work up for Cushing's syndrome can be very confusing and frustrating at times for the patient and their physicians. Doing a meticulous work up is necessary to reach an accurate conclusion. Misdiagnosing Cushing's can lead to a