or the cortical compartment. Lastly, we tail-suspended 5.5 month old male mice and sacrificed them 21 days later. E06-scFv transgenic mice had similar cortical bone loss compared to WT mice. In conclusion, the E06-scFV transgene attenuates the age-associated cancellous bone loss in both female and male mice, but has no effect on the OVX- or unloading-induced bone loss. These results fully support our hypothesis that an increase in PC-OxPLs with age, caused at least in part by a decrease in natural anti-PC antibodies, contributes to the age-associated bone loss. This evidence provides proof of concept that blocking PC-OxPLs represents a therapeutic approach to countering the increase of PC-OxPLs with age and their adverse effects on age-related bone loss as well as atherosclerosis and NASH. It also confirms that the mechanisms of cancellous and cortical bone loss are distinct.

Bone and Mineral Metabolism

BONE AND MINERAL METABOLISM MISCELLANEOUS

Chronic Stimulation of Arcuate Kiss1 Neurons Decreases Bone Mass in Female Mice

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Loss of peripheral estrogen in postmenopausal women is often associated with decreased physical activity and loss of bone mass, leading to an increased risk of metabolic diseases, osteoporosis, and skeletal fragility. While it is well-established that loss of peripheral estrogen signaling results in bone loss, we previously found that eliminating central estrogen signaling paradoxically results in an unexpected massive increase in bone mass only in female mice. Specifically, deletion of estrogen receptor alpha (ERα) signaling in kisspeptin 1 (Kiss1) expressing neurons of the arcuate nucleus (ARC^{Kiss1}) increases bone mass at the expense of reproduction in female mice. Currently, the mechanisms and the neurocircuits that modulate these unexpected responses are unknown. Here, to begin addressing these questions, we asked if changing the neuronal output of ARC^{Kiss1} neurons using chemogenetic manipulation of ARC^{Kiss1} neurons might also alter bone mass and locomotion in female mice. To do this, we delivered stimulatory (AAV2-hM3Dq-mCherry) designer receptors exclusively activated by designer drugs (DREADDs) to the ARC of wild type and Kiss1-Cre+ ($Kiss1\text{-}Cre^{hM3q\text{-}DREADDs}$) female mice and asked if chronic activation of ARC^{Kiss1} neurons might alter bone mass as analyzed by standard ex-vivo μCT imaging. Clozapine N-oxide (CNO) was delivered for 22 days (0.1 mg/mL). We also leveraged the ANY-Maze system to assess home cage activity over an extensive 96-hour period. Acute activation of ARC^{Kiss1} tended to decrease home cage activity by nearly 40% in $Kiss1\text{-}Cre^{hM3q\text{-}DREADDs}$ mice during the dark period compared to WT females. Interestingly, chronic activation of ARC^{Kiss1} neurons significantly lowered trabecular bone volume by nearly 30%. Current studies are underway to ask if inhibiting ARC^{Kiss1} neurons results in increased bone mass. Our findings collectively suggest that the neuronal activity of ARC^{Kiss1} neurons is sufficient to shift energy allocation away from locomotion and bone-building to maximize reproductive capacity. We speculate that the widely used SERM in breast cancer treatment, Tamoxifen, might exert its bone sparing effect by silencing ARC^{Kiss1} neurons.

Bone and Mineral Metabolism

BONE AND MINERAL METABOLISM MISCELLANEOUS

Comparative Transcriptomic Profiling Revealed Distinctive Patterns in Differentially Expressed Genes Related to Clinicopathologic Features of Parathyroid Carcinoma and Adenoma

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Parathyroid carcinoma is a rare malignancy which remains as a clinical unmet need lacking effective therapeutic intervention. (1) In this study, we compared mutational profile of parathyroid carcinoma, adenoma, and normal parathyroid tissue using RNA-Seq based transcriptomics analysis and whole exome sequencing. A total of 40 parathyroid specimens [parathyroid carcinoma (n=8), adenoma (n=24), and normal tissue incidentally obtained from thyroidectomy for various reasons (n=8)] from 39 individuals (women n=34, 87%; mean age 51 year) were analyzed. Compared to adenoma and normal parathyroid groups, parathyroid carcinoma group had younger age (carcinoma 35 ± 12 vs. other 56 ± 16 year, p=0.001) and higher serum parathyroid hormone (PTH; 231 [145–474] vs. 114 [88–196] vs. 34 [29–41] pg/mL, p=0.001) prior to surgery. CDC73 mutation was found in 7 of 8 carcinoma specimens, which harbored germline mutation in 6 of them. Among top feature gene mutations for classifying adenoma and carcinoma, carcinoma-specific genes showed high specificity, whereas adenoma-related key features were largely overlapped with normal tissues. Transcriptional profiling revealed 546 carcinoma-specific differentially expressed genes (DEGs), 135 adenoma-specific DEGs, and 323 common DEGs. Hierarchical clustering with 546 carcinoma-specific DEGs detected four clusters with distinctive clinicopathologic characteristics (cluster 1 [n=12]: 7 normal tissues and 5 adenomas; cluster 2 and 3 [n=22]: all adenomas except one normal tissue; cluster 4 [n=9]: all parathyroid carcinomas except one adenoma). Carcinoma-specific DEGs include upregulation of GRIN2A, LYPD1, and SOX2 and downregulation of ENTPPL, MYO3B, and PIK3C2G. Gene ontology enrichment revealed that these DEGs were mainly involved in the binding of cell adhesion molecule, actin, and Rho GTPase, and extracellular matrix