Defect Repair in Bisphosphonate-treated Osteoporotic Bone

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Bisphosphonates (BPs) are inhibitors of bone resorption used in the treatment of postmenopausal osteoporosis. Since bone remodelling is critical in fracture healing, it is hypothesized that long-term therapy with BP will impair the bone's ability to repair fractures. To test this hypothesis, 12 week old mice were ovariectomized (OVX). After 8 weeks, mice were injected twice weekly with the BP Alendronate (ALN) until sacrifice. Bone density was evaluated by peripheral quantitative computer tomography (pQCT). After 5 weeks after the onset of ALN injections, femoral bones were osteotomized and rigidly (MouseFix™; RIS) or non-rigidly (FlexiPlate™; RIS) fixed. Femora (experimental & contralateral) were collected 1 and 5 weeks post-osteotomy for histological and microCT analysis. Total RNA was isolated from the tissues of the defect site 3, 7, 14 and 28 days after osteotomy for sequencing.

Analysis of the transcriptome revealed that the stability of the fixation at the repair site is the condition that exerts the strongest effects on the number of differentially expressed genes (DEG) over the entire time course (between 9k to 17k DEG). Alendronate was found to be the condition exerting the second strongest effects on the transcriptome, leading to an increase in the number of DEGs over time (2k DEG at day 28). Finally, less than 200 DEGs were detected when transcriptomes from sham and OVX animals were compared. To assess the kinetics of repair in dependence of rigidity of fixation and ALN treatment, Principal Component Analysis of the top 1000 DEG was performed. The analysis revealed that repair was delayed in bones with non-rigidly fixed osteotomies and the delay was amplified in ALN treated animals. Gene ontology related path analysis using EBSeq-HMM and Panther revealed GO terms describing chondrogenic pathways to be fully dependent on the rigidity of the fixation of the osteotomy. ALN, on the other hand, affected primarily GO terms describing osteogenic pathways in repair tissues from rigidly fixed osteotomies and chondrogenic pathways after non-rigid fixation, respectively. The data suggests that stability and treatment with BP synergistically act in the delay of bone repair.