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The role of PAR2 in osteoblast differentiation vs osteoblast function.

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Studies have revealed a bone-specific role for protease activated receptor 2 (PAR2) in the development of murine osteoarthritis. Notably, the absence of PAR2 leads to reduced osteosclerosis and osteophytogenesis. Although PAR2 can enhance osteoblast differentiation and callus formation during repair, there is no evidence for a role in the maintenance of the adult skeleton. The aim of this study was to investigate the role of PAR2 in mature osteoblasts. Osteoblast-PAR2 conditional knockout mice (PAR2<sup>ob/ob</sup>) were generated, and femur and tibia profiled at 5, 14 and 62-weeks. At 5-weeks, PAR2<sup>ob/ob</sup> showed significantly lower trabecular bone density (7.6%±0.9) in comparison to floxed controls (11.9%±2.4)(P=0.01). However, this difference resolved by 14-weeks. Aged mice (62-weeks) showed progressive bone loss, however, this was inconsistent across the floxed and PAR2<sup>ob/ob</sup>. Controls lost 51% of trabecular bone whilst PAR2<sup>ob/ob</sup> only lost 35% (P=0.004). To investigate additional cellular contributors to skeletal maintenance, chondrocyte-specific PAR2 knockouts were also generated and profiled. In this setting the opposite effect was observed; i.e., trabecular bone density was the same at 5-weeks and significantly decreased after 14-weeks. Providing a potential explanation for the lack of a bone phenotype in adult PAR2-global knockout mice. Finally, *in vitro* studies were undertaken to investigate mineralisation in a range of osteoblast states (i.e., bone marrow, neonatal calvarial osteoblasts and aged osteoblasts extracted from long bones). In the absence of PAR2, bone marrow cultures and neonatal calvarial pre-osteoblasts showed significantly lower alkaline phosphatase (WT 86.6±18, PAR2<sup>-/-</sup> 47.6±4, P=0.02) and mineralisation (WT 5.3±2.7, PAR2<sup>-/-</sup> 12.2±5, P=0.02), whilst mature differentiated aged osteoblasts had a 2 fold increase in mineral formation (P=0.03). In summary, these data highlight the difference between osteoblast differentiation and function, as well as the importance of age in the osteoblast. We hypothesise that whilst PAR2 enhances osteoblast differentiation, it inhibits the function of mature osteoblasts.