15 SUSTAINED PI3-KINASE ACTIVITY IN MYELOID CELLS ENHANCES OSTEOCLASTOGENESIS AND AUGMENTS LOCAL BONE DESTRUCTION

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Systemic bone loss in diseases such as osteoporosis or local bone destruction in rheumatoid arthritis, proriasis arthritis or ankylosing spondylitis often leads to disability and severely reduced quality of life. This damage to the bony structures is almost exclusively mediated by a special cell type, the osteoclasts. Therefore, it is important to understand factors and pathways regulating the generation of osteoclasts. In this study, the authors analysed the impact of the PI3-Kinase/PTEN axis on osteoclast generation and bone biology under basal and inflammatory conditions. PTEN is a lipid phosphatase and one of the main antagonists of the PI3-kinase. The authors show that mice with a monocyte/macrophage-specific deletion of PTEN (myeloid specific PTEN$^{-/-}$) display increased osteoclastogenesis in vitro and in vivo compared to wild-type mice. However, under homeostatic conditions, enhanced osteoclastogenesis did not result in systemic bone loss. This was most likely due to a significantly increased bone formation evidenced by an enhanced mineral apposition rate in myeloid specific PTEN$^{-/-}$ mice, whereas osteoblast numbers were not different. In contrast, under inflammatory conditions in the hTNFtg mouse model of arthritis, myeloid specific PTEN$^{-/-}$ displayed enhanced local bone destruction as well as osteoclast formation in the inflamed joints. The extent of synovial inflammation, however, was not different between wt and myeloid specific PTEN$^{-/-}$ mice.

These data demonstrate that enhanced PI3-Kinase activity in myeloid cells leads to increased osteoclastogenesis. Under homeostatic conditions, increased osteoclastogenesis is compensated by enhanced osteoblast activity. However, under inflammatory conditions, loss of control of PI3-Kinase activity by PTEN in myeloid cells leads to enhanced local bone destruction.