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PTEN downregulation in mouse osteoprogenitor cells impacts on bone stability and turnover

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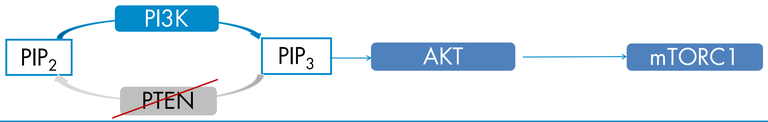
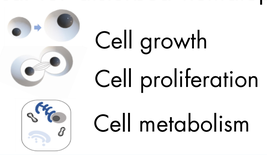
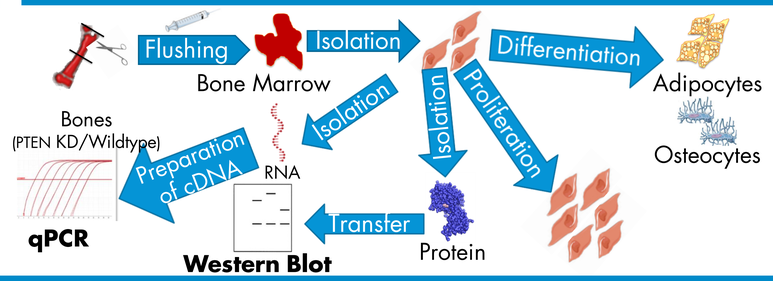
Background & Aim

PTEN is a tumor suppressor gene, that negatively regulates the growth-promoting PI3K (phosphoinositide 3 kinase)/AKT(protein kinase B)/mTORC1(mechanistic Target of Rapamycin complex 1) cascade. Signaling through the PI3K/AKT/mTORC1 pathway modulates bone development and remodeling. Using an animal model with Pten insufficiency, we aimed to further identify factors that are causal for disturbed hematopoiesis and bone distribution disorders related to Pten knockdown (KD) mutation.





Methods



Conclusion & Outlook

PTEN downregulation in Osterix-expressing cells increases bone stability and elasticity and leads to increased proliferation and osteogenic differentiation. We aim to evaluate changes in bone turnover in Pten KD mice compared to wildtype (WT) mice using calcein labeling.

Results

PTEN KD influences PI3K signaling.

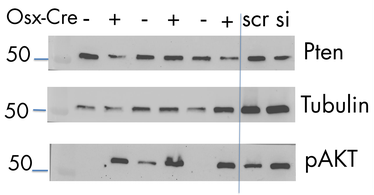


Figure 1: *PTEN protein in Pten KD bones is downregulated compared to control mice. AKT phosphorylation is upregulated (downstream PI3K signaling activation). Tubulin used as loading control.*

PTEN KD enhances proliferation.

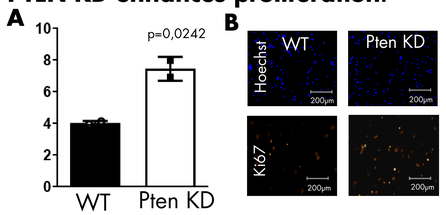


Figure 2: *Proliferation (A) and Ki-67 positive fraction (B) increased in Pten KD bone marrow stromal cells compared to control mice.*

PTEN KD increases marrow adipocytes.

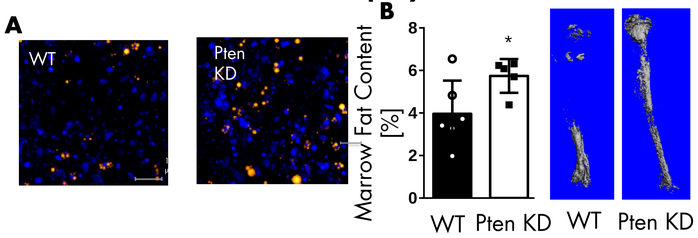


Figure 3: *Osmium staining (A) revealed increased amount of adipocytes in mature Pten KD bones. Lipid accumulation (B) increased in PTEN KD cells after 14 days of adipocyte differentiation.*

Osteogenesis is enhanced in Pten KD BMSCs.

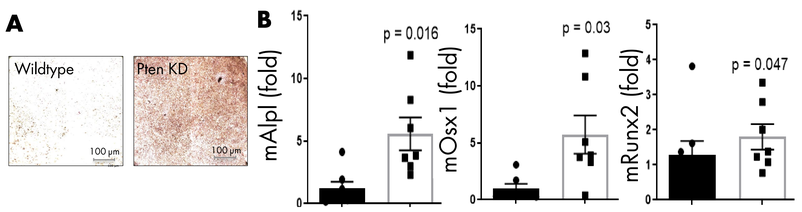


Figure 4: *Osteogenic differentiation (A) of Pten KD BMSCs increased and bone markers increased on mRNA level after 14 days of cell culture.*

Bone remodeling is influenced in Pten KD bones.

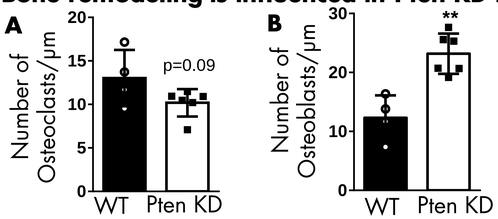


Figure 5: *Osteoclasts (A) are decreased while Osteoblasts (B) are increased in Pten KD bones.*

PTEN KD increases bone turnover.

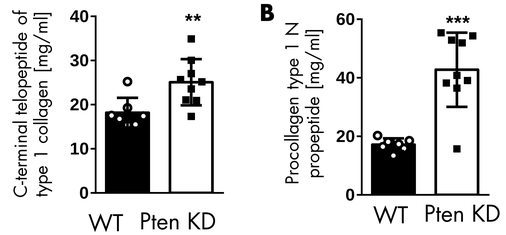


Figure 6: *Bone resorption (A) and bone formation (B) are increased in PTEN KD cells.*

PTEN KD influences bone structure and bone phenotype.

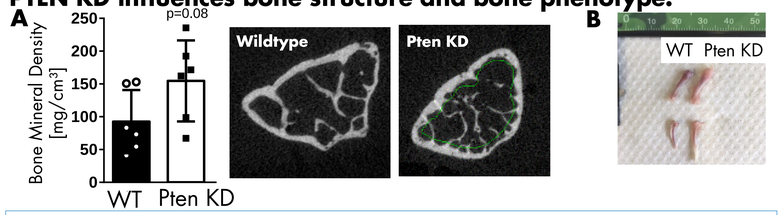


Figure 7: *Pten KD bones illustrate higher trabecular bone mineral density (A) and are more pale (B) than WT bones.*

PTEN KD increases mechanical strength.

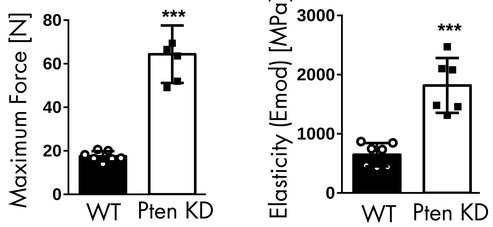


Figure 8: *Maximum Force (A) and Elasticity (B) are increased in Pten KD bones compared to WT.*

References
[1]Haddadi et.al. Toward Systems Pathology for PTEN Diagnostics. Cold Spring Harbor perspectives in medicine (2019)
[2]Filtz, E.A. et al. Rb1 and Pten Co-Deletion in Osteoblast PrecursorCells Causes Rapid Lipoma Formation in Mice. PloS one 10,(2015)

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