Protective effect of PTH signaling in osteocytes from oxidative stress and cellular senescence

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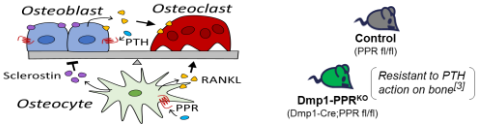
Background

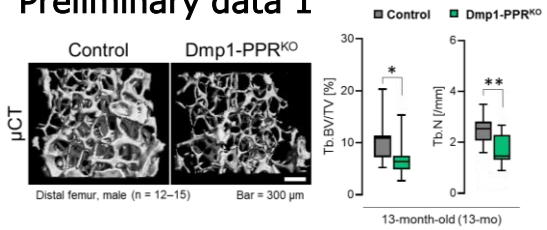
Age-related osteoporosis is characterized as decline in bone formation and increase in bone resorption[1].

Parathyroid hormone (PTH) is clinically used anabolic agent to treat osteoporosis[2].



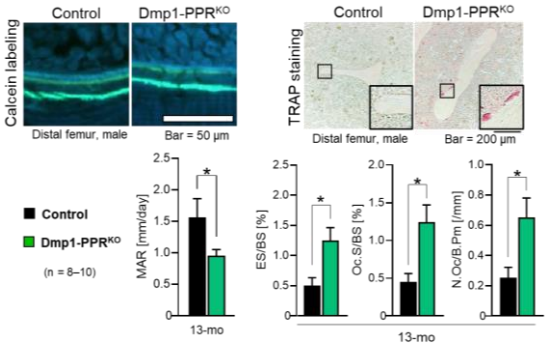
The role of PPR signaling in osteocytes in age-induced osteoporosis is still unknown.

Preliminary data 1



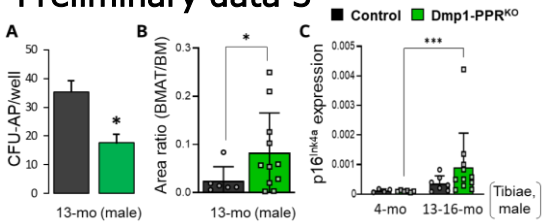
Trabecular bone volume and number was significantly reduced in aging Dmp1-PPR^{KO} mice compared to control

Preliminary data 2



Accelerated bone loss in aging Dmp1-PPR^{KO} was due to reduced bone formation and increased bone resorption

Preliminary data 3



Aging Dmp1-PPR^{KO} mice promote skeletal senescence demonstrated as (**A**) depletion of osteoprogenitors, (**B**) marrow adiposity, and (**C**) p16^{Ink4a} upregulation

Hypothesis

- *Aging accumulates reactive oxygen species (ROS)*[4]
- *Oxidative stress causes cell apoptosis and senescence*[5]

PPR signaling in osteocytes prevents age-induced bone loss by protecting osteocyte from ROS-induced oxidative stress

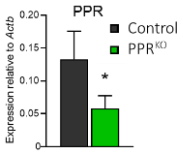
Aim

Examine the role of PPR signaling in osteocytes on oxidative stress-induced cell death and senescence

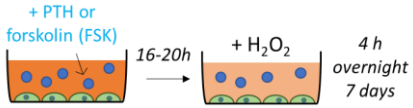
Materials/Methods

Cell

Osteocytic cell line lacking PPR (Ocy454-12H PPR^{KO}) was established by using CRISPR/Cas9



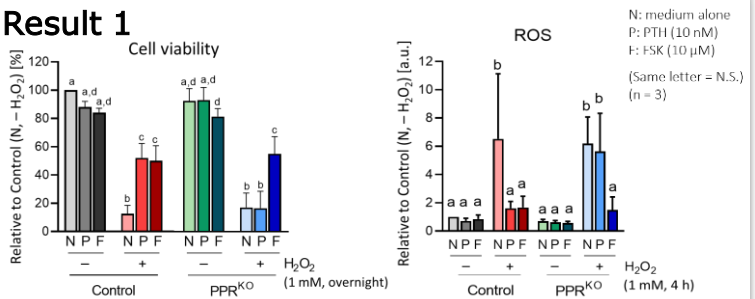
Treatments



Analysis

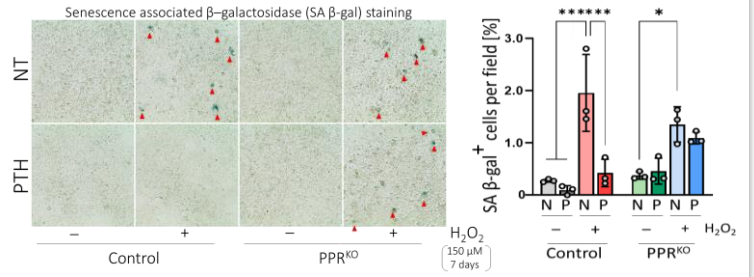
- Cell viability assay
- Intracellular ROS detection
- Senescence-associated β-galactosidase staining
- mRNA expression (real time qPCR)

Result 1



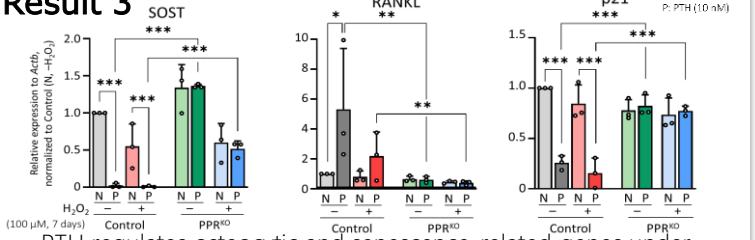
PTH protects osteocytes from H_2O_2-induced death by suppressing ROS accumulation

Result 2



PTH suppresses oxidative stress-induced senescence in osteocytes

Result 3



PTH regulates osteocytic and senescence-related genes under oxidative stress

Conclusion

PPR signaling protects osteocytes from H_2O_2-induced cell death and senescence, in part, due to suppression of ROS and p21, respectively

References: [1] Demontiero *et al., Ther Adv Musculoskelet Dis*, 2012., [2] Shoback *et al., N Engl J Med*, 2008., [3] Saini *et al., J Biol Chem*, 2013., [4] Gruber *et al., Exp Ger*[illegible] 2006., [5] Kitase *et al., Cell Rep*, 2018.