PREMATURELY AGED POLGA MICE EXHIBIT DEGENERATED OSTEOCYTE NETWORK AND MECHANOSENSATION

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Introduction

Age-related osteoporosis is a major problem in human musculoskeletal health and has proven difficult to model in mice. Osteocytes, key mechanosensors of bone, have emerged as an important target for preventing age-related osteoporosis, characterized by decreased bone mass over time. This decrease results from the morphological changes in the osteocyte lacunocanalicular system (OCLN) and their diminished ability to sense mechanical stress [1]. PolgA$^{D257A/D257A}$ (PolgA) mice exhibit a naturally accelerated aging phenotype at 40 weeks with an early onset of clinically-relevant musculoskeletal aging characteristics, including frailty and osteosarcopenia [2]. However, the relevance of this model - as a model for age-related osteoporosis and to understand the responsible mechanism of age-associated changes in the OCLN - remains unclear. Here we demonstrate age-and sex-related bone changes and associated degeneration of the osteocyte network in both female and male PolgA mice.

Methods

Bone morphometric parameters were evaluated from the right femurs of homozygous female and male PolgA mice (n=9-11/group) and wild-type (WT) littermates (n=9-16/group) by micro-CT (voxel size: 10 µm). Changes in the bone structure were correlated with alterations in osteocyte density and dendriticity. Osteocytes and their dendrites were imaged with 3D confocal microscopy on Phalloidin-Hoechst-stained sections of PolgA mice (n=2-4/group), and the WT littermates (n=2-4/group) at 20 and 40 weeks. ImageJ and IMARIS software were used to quantify the osteocyte density and dendriticity from the confocal image stacks. Two-way ANOVA with Tukey corrections was used for statistical analysis.

Results

Micro-CT analysis revealed statistically significantly lower apparent volume density (AVD) in 40-week-old PolgA mice compared to age-matched WT (males: -25%, females: -15%) and 20-week-old PolgA mice (males: -24%, females: -19%) (Figure1A). Quantifying confocal image stacks demonstrated a notable decrease in the number of dendrites per osteocyte in 40-week-old PolgA mice compared to aged-matched controls (males: -31%, females: -52%) and young PolgA (20-week-old males: -45%, females: -56%) (Figure 1B-C) indicating osteocyte network disruption in the PolgA mice at 40 weeks.

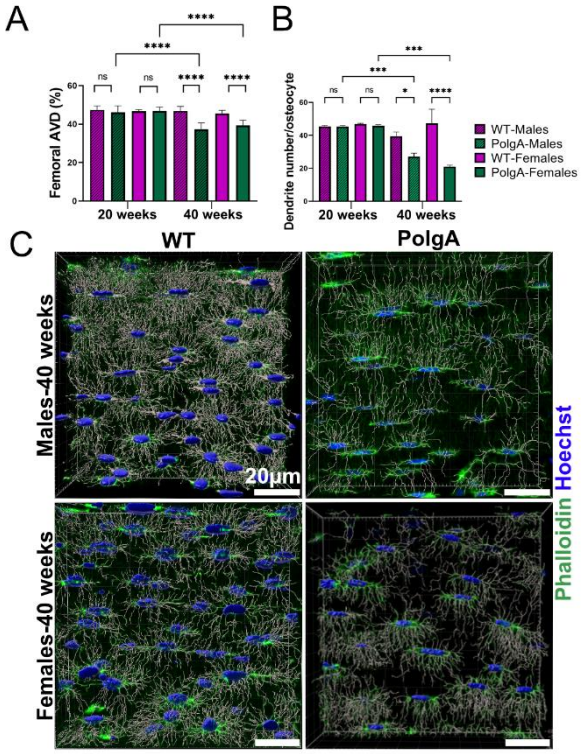

Figure 1: Age-related changes in the bone and osteocyte network in 40-week-old PolgA mice compared to WT littermates A) decreased femoral AVD, B) reduced number of dendrites per osteocyte, C) degenerated osteocyte connectivity.

Discussion

Our results demonstrate age-related degeneration in bone architecture in PolgA mice. Furthermore, we found that the dendrite numbers per osteocyte decreased with age in both female and male PolgA mice, with greater reduction in females compared to males. Since similar age-related degeneration of the bone and osteocyte network has been observed in humans [3], our results suggest that the PolgA mouse could be a robust model for investigating molecular mechanisms responsible for age-related osteoporosis.

References

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