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# Aging intervention by targeting the H-type vasculature and its role in cell fate decision

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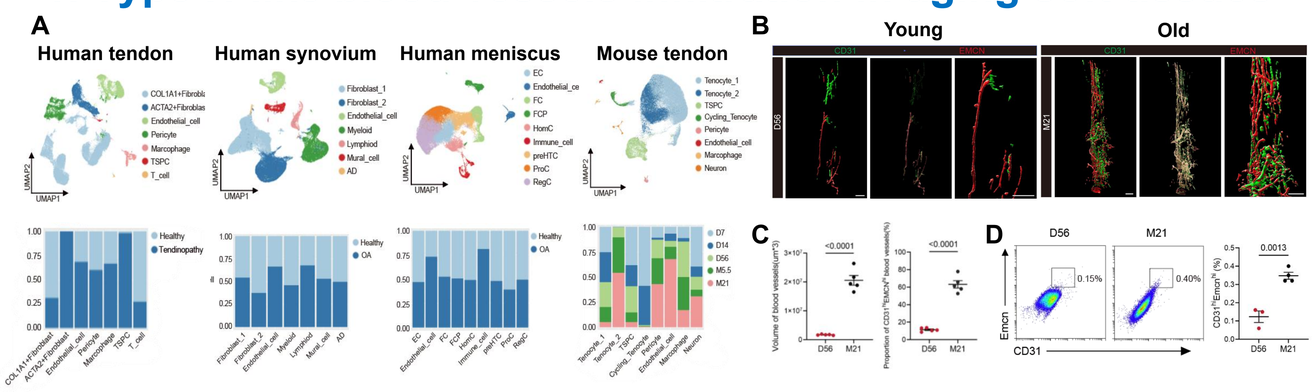
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## BRIEF INTRODUCTION

Aging manifests with distinct characteristics across different tissues. Although vascular decline is a recognized driver of hard tissue aging, its role in soft tissue degeneration remains poorly defined. This study aims to characterize specific vascular alterations, identify key cellular subgroups and underlying regulatory mechanisms in aging soft tissues. Our investigation revealed an increase in type H-like blood vessels in aging soft tissues for the first time. We identified Coch+ subpopulation as a key driver of vascular infiltration through the secretion of angiopoietin 2(ANG2) and VEGF-A. Notably, reducing type H-like blood vessels or inhibiting ANG2/VEGF-A in aging mice, we observed delayed soft tissues aging and improved locomotor function.

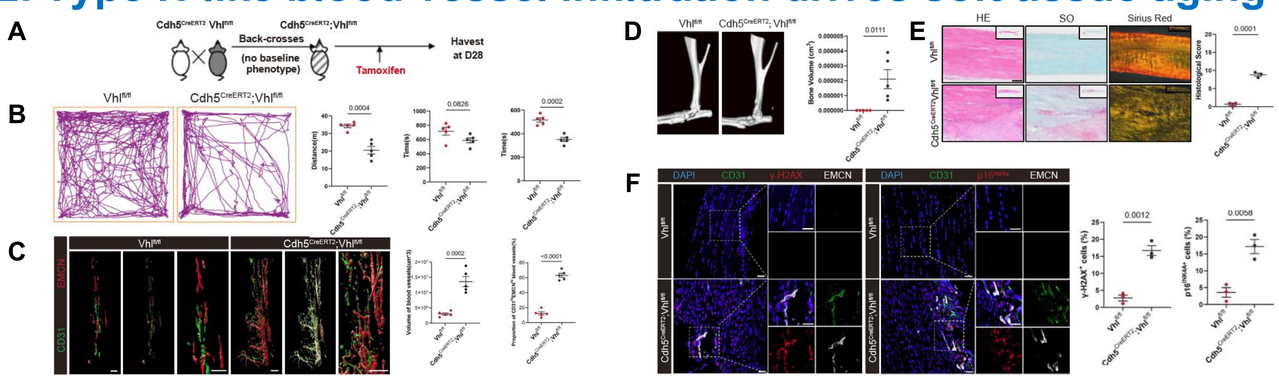
## RESULTS

### 1. Type H-like blood vessels infiltration in aging soft tissues



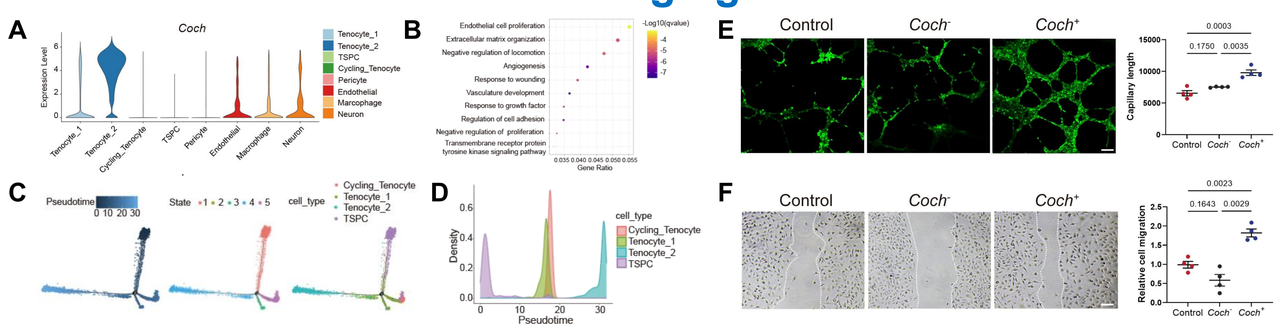

(A) scRNA-seq clustering and corresponding cell proportions (B) Whole-mount clearing imaging of mouse tendon vessels (C) Quantitative analysis of vessels (D) Flow cytometry of endothelial cells

### 2. Type H-like blood vessel infiltration drives soft tissue aging



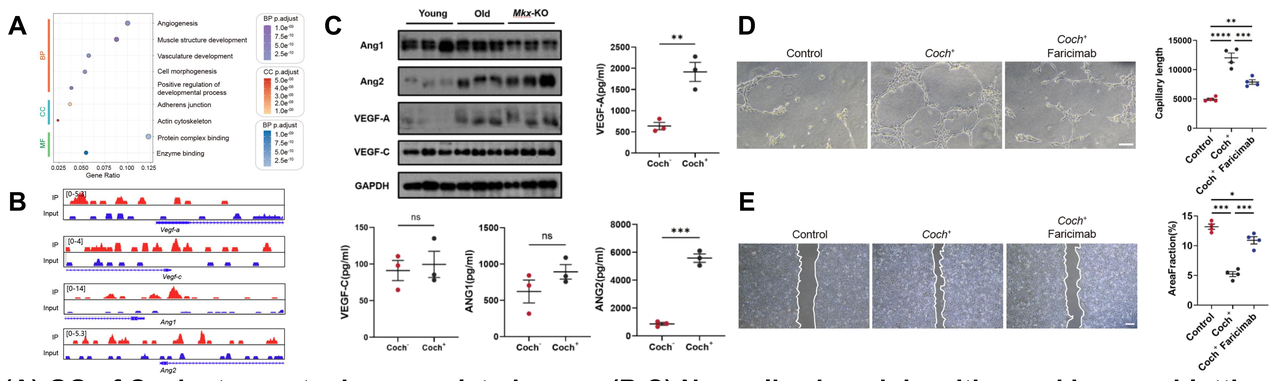

(A) Cdh5$^{CreERT2}$-Vhl$^{fl/fl}$ and Vhl$^{fl/fl}$ mice (B) Behavioral test (C) Whole-mount clearing imaging of tendon vessels (D) μCT (E) Histology (F) Immunofluorescent staining of CD31, EMCN, p16$^{INK4a}$ , γ-H2AX

### 3. Accumulation of Coch+ tenocytes promotes vascular infiltration in aging tendons



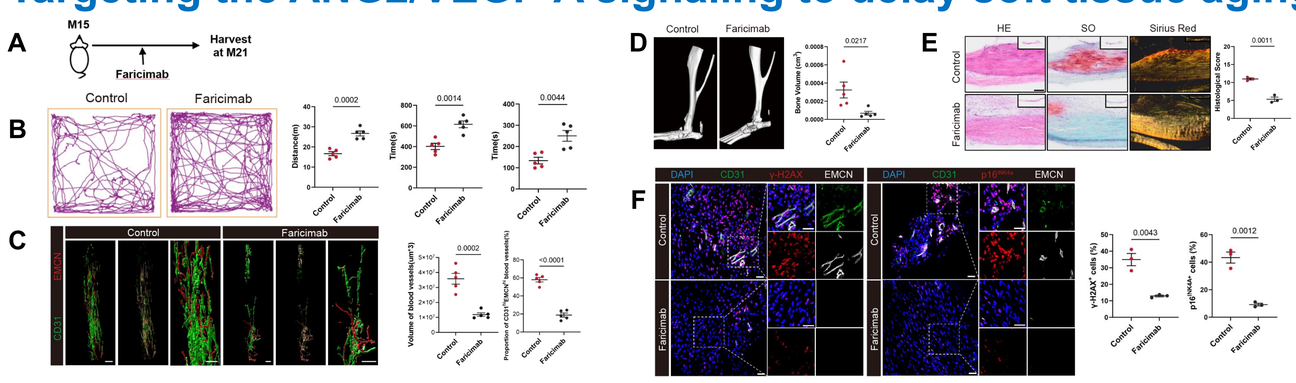

(A) Violin plot of Coch expression (B) GO terms of Coch+ tenocyte DEGs (C,D) Cell maturation trajectory (E,F) Tube formation and endothelial migration experiment with Coch+ conditioned medium

### 4. Coch+ tenocytes promote angiogenesis via ANG2/VEGF-A




(A) GO of Coch+ tenocyte downregulated genes (B,C) Normalized read densities and immunoblotting of VEGF-A, VEGF-C, ANG1, and ANG2 (D,E) ANG2/VEGF-A Ab in tube formation, endothelial migration

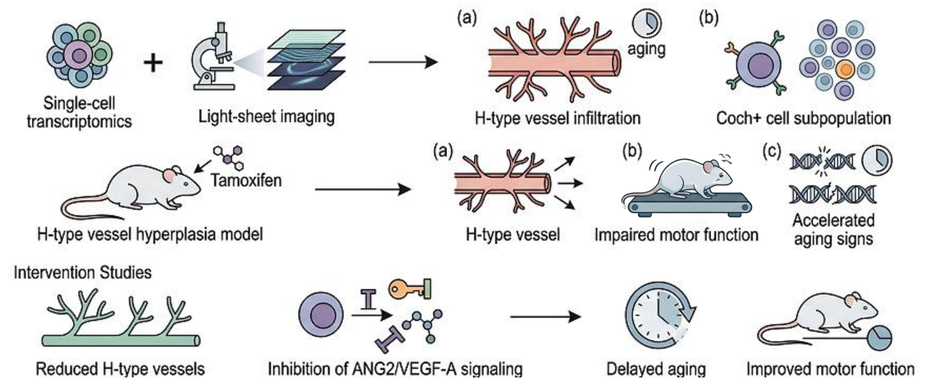
### 5. Targeting the ANG2/VEGF-A signaling to delay soft tissue aging




(A) ANG2/VEGF-A Ab injection (B) Behavioral test (C) Whole-mount clearing imaging of tendon vessels (D) μCT (E) Histology (F) Immunofluorescent staining of CD31, EMCN, p16$^{INK4a}$ , γ-H2AX

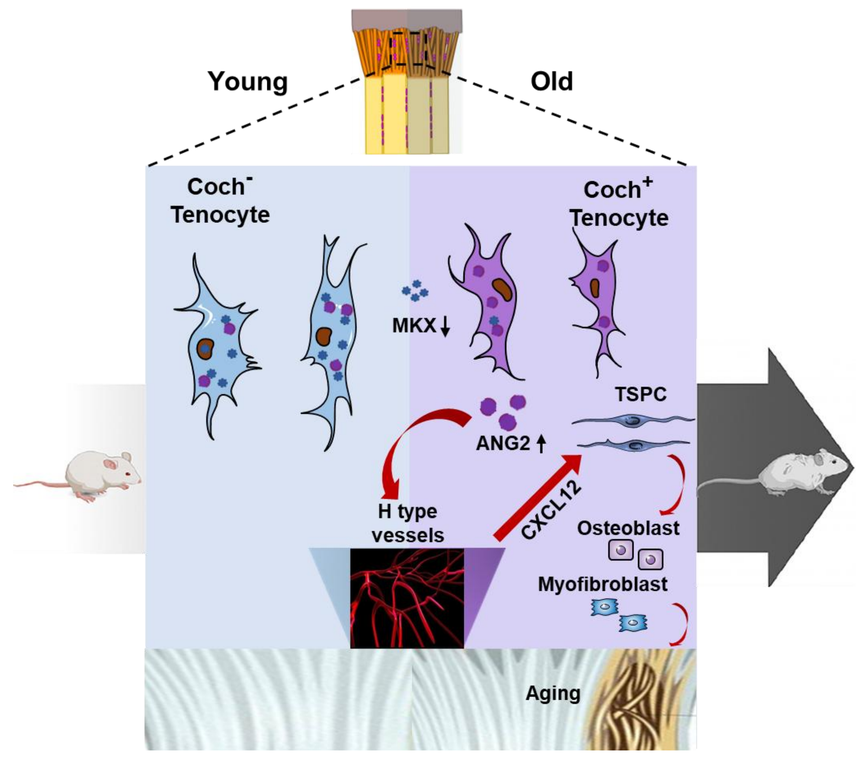
## METHODS

Using scRNA-seq and light sheet imaging, we characterized age-related soft tissue vascular changes and identified vessel-associated subpopulations. Using transgenic mouse models, we determined the function of type H vessels. Finally, we targeted type H vessel-related signaling pathways to delay aging.




## CONCLUSIONS

These findings reveal a novel mechanism linking vascular infiltration and pathological cell fate transitions in soft tissue aging, highlighting the therapeutic potential of targeting the coupling of type H-like blood vessels and cell fate transition to delay soft tissue aging.




## ACKNOWLEDGEMENT

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