Transcriptomic Changes During the Replicative Senescence of Human Articular Chondrocytes in Postmenopausal Osteoarthritis

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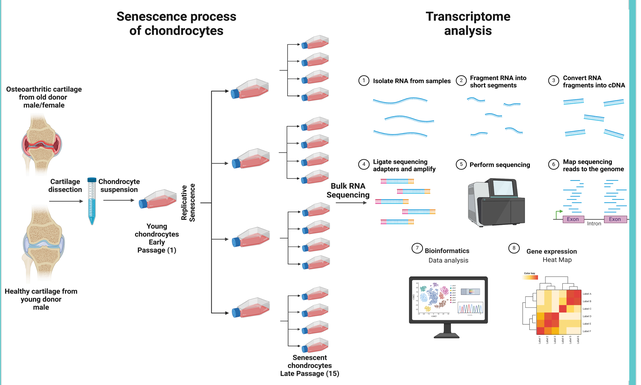
BACKGROUND

Osteoarthritis (OA) is a degenerative joint disease and a leading cause of disability worldwide. OA is characterized by cartilage degradation, joint inflammation, and bone remodeling [1]. Age is a significant risk factor for developing OA, such that over 50% of people who are 65 or older have OA. Intriguingly, the age-related incidence of OA is the same for men and women until the age of menopause. However, after menopause, the incidence of OA in women increases dramatically [2]. Articular cartilage is an estrogen-sensitive tissue, demonstrating sex-related disparities regarding the prevalence and clinical outcomes of OA pathology [3].

The underlying cellular and molecular mechanisms that contribute to post-menopausal OA remain unknown. There is a critical need to explore these sex differences in OA to further develop effective personalized strategies. Therefore, the overall objective of this study is to investigate the relationship between sex-related determinants of OA, with particular focus on the molecular and cellular aspects of chondrocyte aging, which significantly contribute to OA development.

METHODS

Chondrocytes were obtained from the knees of three individuals: two older individuals (ages 72 and 80) diagnosed with OA and one young adult (age 26) without OA. Chondrocytes from all donors were cultured and serially passaged until they reached replicative senescence. RNA-sequencing was then performed to identify transcriptomic changes associated with cell passage.



RESULTS

Figure 1

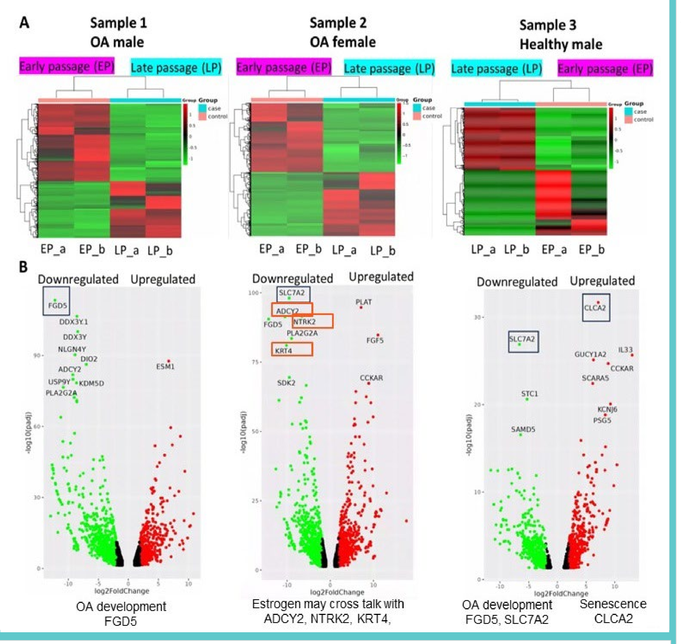


Figure 3

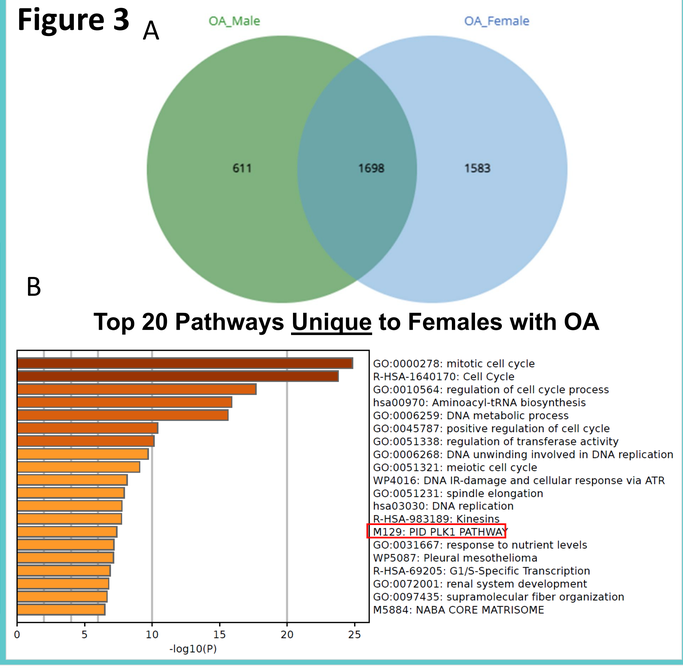
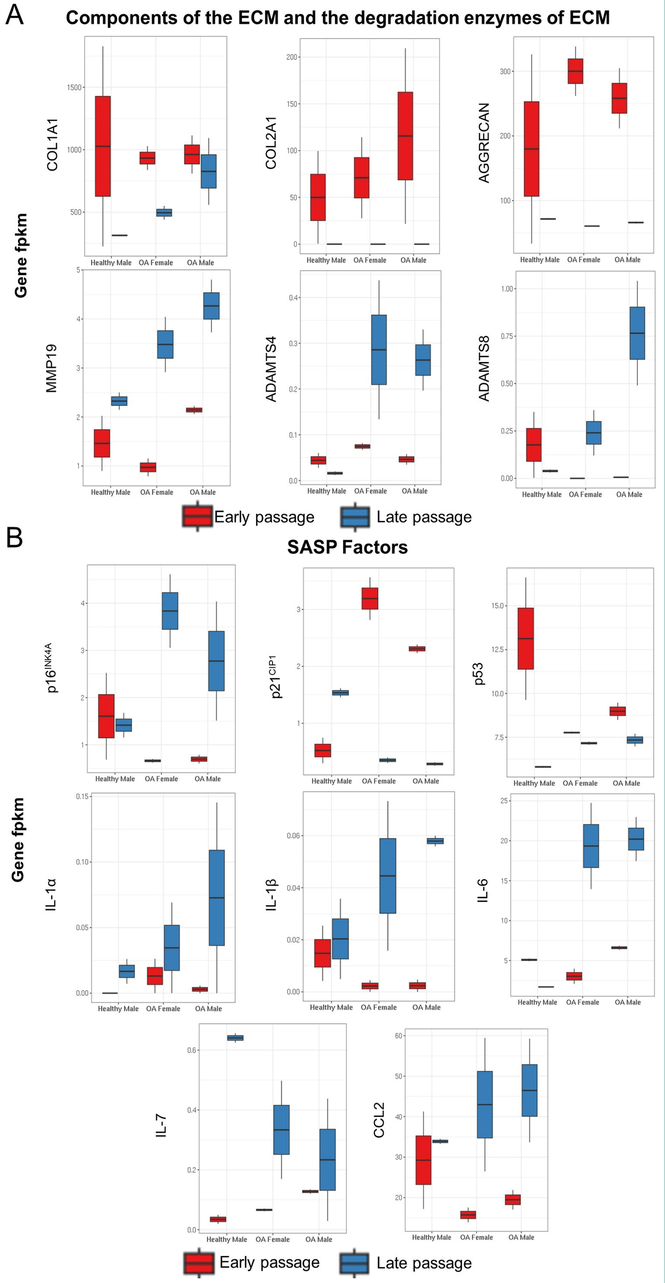


Figure 2



DISCUSSION

1.Gene Expression Patterns:

•Distinct differentially expressed genes between:

- Early and late passage chondrocytes
- Males and females
- OA and non-OA samples

2.Volcano Plot Analysis Revealed:

•OA development-related genes: FGD5, SLC7A2

•Cellular senescence gene: CLCA2

•Estrogen-regulated genes: ADCY2, NTRK2, KRT4

3.Senescence and Inflammation Link (SASP):

•Upregulation in late passage OA chondrocytes:

- Inflammatory markers: IL-1α, IL-1β, IL-6, IL-7
- Senescence marker: p16.

4.Extracellular Matrix (ECM) Changes:

•Significant downregulation:

- Type 2 collagen (Col2A1)
- Aggrecan core protein

•Upregulation of matrix-degrading enzymes:

- MMP19, ADAMTS4, ADAMTS8

5.Sex Differences in OA Pathology:

•PLK1 may play a key role in the sex differences observed in OA pathology, particularly through its effects on estrogen responses.

CONCLUSION

- Confirmed age-related molecular changes in chondrocytes during replicative senescence.
- Identified sex-specific differences in gene expression and pathways.

FUTURE DIRECTIONS

- Determining effects of estrogen on senescent chondrocytes.
- Identifying cellular mechanisms of estrogen on IL-1 signaling pathway.
- Focusing on senescence dynamics and cartilage regeneration.

REFERENCES

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3. Dennison EM. Maturitas. 2022;165
- Illustration was created with BioRender.com

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