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Steroid Hormones and Receptors

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A Unique Estrogen-Sensitive Fibroblast Population Drives Abdominal Muscle Fibrosis

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Weakening of the lower abdominal wall muscle via fibrosis causes visceral contents to bulge out, forming inguinal hernias. Humanized aromatase (Aromhum) transgenic male mice develop this weakness in the lower abdominal muscle (LAM) tissue, characterized by extensive fibrosis, muscle atrophy, and scrotal hernias. This mouse model incorporates the human version of the aromatase gene allowing for excessive estradiol (E2) production in skeletal muscle tissue. We have previously shown that the LAM fibroblasts are sensitive to local E2 production due to high levels of estrogen receptor alpha (ERα, Esr1)[1]. Here, we explore the origins of estrogen-driven muscle fibrosis in the LAM tissue of Aromhum mice at a single-cell level.

Wild-type (WT) and Aromhum LAM tissues were processed via single-cell RNA sequencing (n = 3) and analyzed using Seurat. We observed a total of 22 UMAP clusters, including six fibroblast-like clusters. Five of these clusters express the fibro-adipogenic progenitor (FAP) marker Pdgfrα, and two of them are exclusively found in Aromhum LAM tissues. One Aromhum-enriched cluster highly expresses Esr1 and its downstream estrogen-responsive genes such

as Pgr and Greb1. Pseudo-time analysis suggested that this cluster differentiates into a pathogenic fibroblast cluster characterized by high expression pro-inflammatory (Il33, Il6, Ccl8, C4b) and fibrosis-associated (Mmp3, Cthrc1, Saa3, Ptx3) genes. We further validated our findings via flow cytometry, immunocytochemistry, and western blots in LAM, upper abdominal muscle tissues, and quadriceps of both WT and Aromhum mice. We show that protein levels of Pdgfrα, ERα, Mmp3, C4b are greater in the fibroblasts freshly isolated from LAM tissues of Aromhum mice compared to WT mice. Moreover, Aromhum LAM tissue cell cycle analysis reveals that ~15% of all ERα+ cells are in the G2-S phase compared with <1% of ERα- cells. Overall, we provide an insight into the cell types, genes, and proteins that are dysregulated in the LAM tissues from Aromhum mice with hernias.

Inguinal hernias are found in ~25% of the elderly male population[2]. Using an inguinal hernia mouse model that mimics the hernia pathophysiology of elderly men with estrogen excess and testosterone deficiency, we defined a specific population of estrogen-sensitive fibroblasts responsible for fibrosis and weakening of lower abdominal skeletal muscle tissue associated with hernias. We provide an insight into the specific disease-causing fibroblast populations and molecular targets that may be the basis for future therapeutics to prevent or treat inguinal hernias.

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