DPP4 is a specific surface marker for senescent cells in osteoarthritis cartilage.

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INTRODUCTION: Senescent cells, state of cell proliferation arrest, accumulate in more vertebrate tissues as they age and are found in elderly diseases. Increase in senescent cell that occurs with aging appears to play a major role in driving life-limiting age-related diseases. These senescent cells are also a major factor in OA, senescent chondrocytes were found in cartilage tissue isolated from patients undergoing joint replacement surgery. It has been confirmed that the removal of senescent chondrocytes suppresses development of OA and promotes regeneration by creating an appropriate environment.
To develop or screen effective senolytics for the selective elimination of senescent chondrocytes, it is necessary to understand senescent cell-specific signaling mechanisms by separating them. In this study, we aimed to identify a new senescence marker that enables cell separation in a living state through FACS analysis.
METHODS: Senescent chondrocyte markers were screened using flow cytometry and transcriptomic analysis using National Center for Biotechnology Information Gene Expression Omnibus. Senescence phenotypes, such as senescence-associated-galactosidase (SA-β-gal), proliferation, senescence gene expression, OA phenotypes, such as anabolic and catabolic gene expression, hypertrophic marker expression and histological analysis were evaluated in DPP-4+ chondrocytes. Human cartilage tissue and pellet stained with Safranin-O and DPP4.
RESULTS: 35 candidate genes for surface factors selectively expressed on OA chondrocytes are selected by cell surface marker screening by flow cytometry and transcriptomic analysis. Among the 35 genes, CD28 and DPP4 were significantly upregulated in OA patient. Through analysis of surface markers for non-OA, OA and oxidative stress-induced senescent chondrocytes DPP4 was selected as a final senescent chondrocyte marker (Fig1.). Immunostaining revealed expression of $p16^{INK4a}$ and DPP4 increases in correlation with severity of lesions found in human OA cartilage. FACS analysis showed that DPP4+ chondrocytes were increased in human OA cartilage (Fig.2A-B). FACS-mediated sorting of DPP4+ chondrocytes show increased mRNA expression of p16 and p21 compared with DPP4- chondrocytes from OA cartilage and decreased in proliferation rate (Fig2C-E). Chondrocytes expressing DPP4 exhibited decreased *COL2A1* expression and increased hypertrophic marker *MMP13* expression (Fig2F). And these results confirmed by decreased safranin-O staining of DPP-4+ chondrocytes pellets. These data indicated that DPP4+ senescent chondrocytes may play a role in mediating OA development**.**
DISCUSSION: Our finding shows DPP4 is a potential cell surface marker of senescent chondrocytes, which may aid in understanding the role of senescent chondrocytes in OA development and progression. But the exact mechanisms by which DPP-4 expression leads to chondrocyte senescence or DPP4 upregulation and its downstream pathways are currently unknown, further study is required.
SIGNIFICANCE/CLINICAL RELEVANCE: We suggest DPP4 as senescent chondrocyte markers of OA chondrocytes. And we also propose the therapeutic strategy for OA treatment by selectively removing DPP4+ chondrocytes.

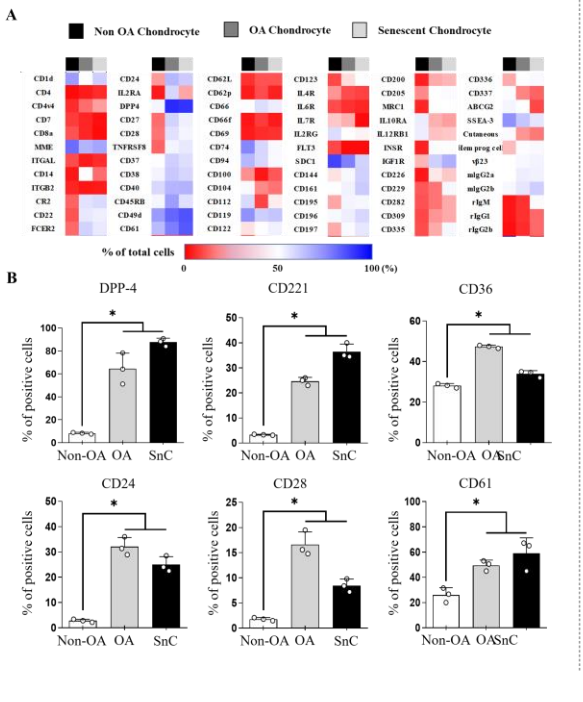

Figure 1. Screening for surface factors selectively expressed on senescent osteoarthritis chondrocytes.

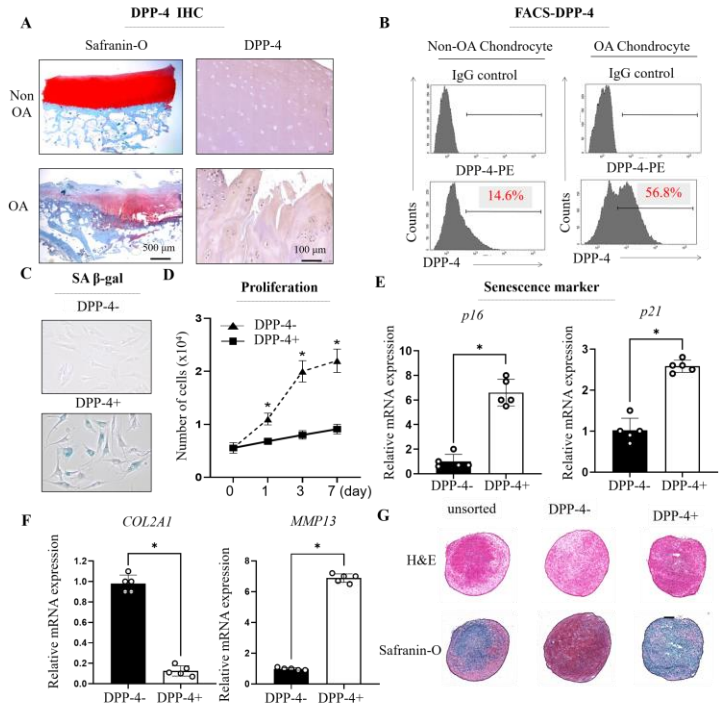

Figure 2. Dipeptidyl Peptidase-4-positive chondrocytes show senescence and osteoarthritis-associated phenotypes.