Selective Targeting of Dipeptidyl-Peptidase 4 (DPP-4) Positive Senescent Chondrocytes with Sitagliptin: In Vitro and In Vivo Efficacy in Osteoarthritis Models

Du Hyun Ro[1], Gun Hee Cho[1], Sung Eun Kim[1,2], Ji Yoon Kim[1], Ha Ru Yang[2], Hee Jung Park[2], Sun Young Wang[2], You Jung Kim[2], Myung Chul Lee[1,2], Hyun Cheol Bae[2]*, and Hyuk-Soo Han[1,2]*

1Department of Orthopedic Surgery, Seoul National University, College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea

2Department of Orthopedic Surgery, Seoul National University Hospital, Yongondong Chongnogu, Seoul 110-744, Korea

Email of Presenting Author: paxgospel@gmail.com

Disclosures: The authors have no relevant financial or non-financial interests to disclose.

INTRODUCTION:

Osteoarthritis (OA) is a prevalent degenerative joint disorder characterized by the wear and tear of articular cartilage, often resulting in substantial pain and disability. One of the cellular hallmarks of OA is the presence of senescent chondrocytes, which have been shown to express dipeptidyl peptidase-4 (DPP-4). Senolytic agents targeting these senescent cells could offer an innovative approach for OA treatment. This research aims to evaluate the efficacy of sitagliptin, a DPP-4 inhibitor, in selectively targeting and eliminating DPP-4+ senescent chondrocytes both in vitro and in an in vivo rat model, thereby potentially mitigating the progression of OA.

METHODS:

This study received ethical approval from the authors' institute. Rat (Wistar) chondrocytes, categorized based on their expression of DPP-4 (DPP-4+ and DPP-4-), were subjected to treatments with various senolytic agents, including sitagliptin, ABT263, 17DMAG, and metformin. The impact on cell viability was evaluated in vitro. A DMM-induced rat OA model was employed for in vivo validation. Intra-articular injections of sitagliptin and the aforementioned agents were administered to gauge their effects on OA progression, cartilage degradation, and subchondral bone thickness. All analyses were performed using GraphPad Prism 8 (San Diego, California, USA). Significance was set at $p < 0.05$.

RESULT:

Sitagliptin effectively reduced the viability of DPP-4+ chondrocytes in vitro without affecting the DPP-4- chondrocyte population. In the DMM-induced rat OA model, sitagliptin markedly prevented cartilage degradation and led to significant improvements in subchondral bone plate thickness. These beneficial effects were substantiated by a notable decrease in OARSI scores in the sitagliptin-treated group when compared to the other treatment modalities. Sitagliptin also improved physical performance in the treated rats, evidenced by an increase in treadmill running time and distance (Sample size: n = 7, * P < 0.05).

DISCUSSION:

Sitagliptin can selectively target DPP-4+ senescent chondrocytes, thereby proving effective in inhibiting OA progression. Building on previous research that identified DPP-4's role in cartilage degradation and chondrocyte senescence, we further validate its therapeutic potential using a DMM-induced OA rat model. However, several limitations exist, such as the lack of understanding of the mechanistic role of DPP-4 in chondrocyte senescence and OA pathology. Additionally, the study was conducted using a young rat model, thus questioning the translatability of these results to age-related OA in humans.

SIGNIFICANCE/CLINICAL RELEVANCE:

This study elucidates that sitagliptin could be a highly promising therapeutic agent for targeted OA therapy. By selectively removing DPP-4+ senescent chondrocytes, sitagliptin has the potential to mitigate cartilage degradation and improve physical performance, thereby offering a new avenue for OA treatment.

ACKNOWLEDGEMENTS:

This work was supported by the New Faculty Startup Fund from Seoul National University (800-2021-0559) and the National Research Foundation of Korea (NRF) grant funded by the Korea Ministry of Science and ICT (MSIT) (NRF-2019R1A2C1009434).

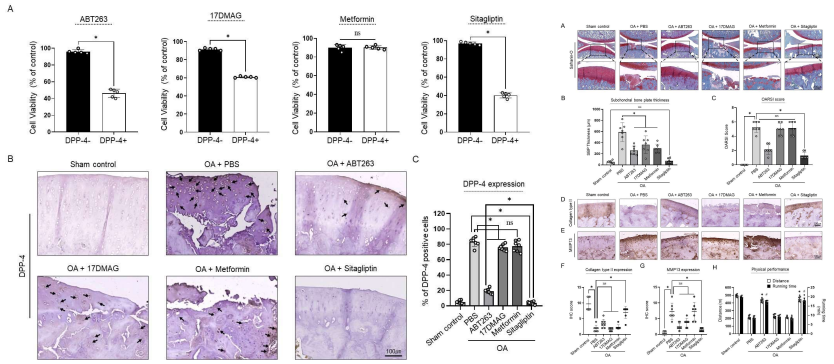

Figure 1. Sitagliptin could specifically and effectively target DPP-4 positive chondrocytes. (A) Evaluation of cell viability of DPP-4- and DPP-4+ chondrocytes upon treatment of 20 μM ABT263, 100nM 17DMAG, 20 μM metformin or 5 μM sitagliptin (n = 5). (B) Representative histological analysis using IHC for DPP-4 staining to evaluate in vivo senolytic effects of ABT263, 17DMAG, metformin and sitagliptin and (C) Quantification of DPP-4 positive cells from the DPP-4 IHC staining (n = 7). * P < 0.05

Figure 2. Intra-articular injection of the DPP-4-inhibitor sitagliptin prevented OA development in the rat DMM model. (A) Representative histological analysis using safranin-O to evaluate OA progression in sham control and DMM rats after PBS, ABT263, 17DMAG, metformin or sitagliptin injection, (B) quantification of subchondral bone plate thickness of sham control and DMM rats after PBS, ABT263, 17DMAG, metformin or sitagliptin injection and (C) scoring of OA using OARSI grading system in sham control and DMM-induced OA rat that had undergone intra-articular injection of PBS, ABT263, 17DMAG, metformin or sitagliptin (n = 7). Representative collagen type II (D) and MMP13 (E) IHC staining images of sham control and DMM rats injected with PBS, ABT263, 17DMAG, metformin or sitagliptin and (F and G) quantification collagen type II and MMP13, respectively, using scoring system (n = 7). (H) Treadmill running distance and time (n = 7), and # and * indicate $p < 0.05$ when compared to PBS groups, respectively. * P < 0.05