Front. Med. 2025, 19(6): 1320−1322
https://doi.org/10.1007/s11684-025-1177-8

COMMENT

Cellular senescence in age-related musculoskeletal diseases: intercellular communication as a driver of disease pathogenesis

Ilya Klabukov (✉)[1], Elizabeth Skornyakova[2], Daria Eygel[1], Denis Baranovskii[1], Peter Shegay[1], Andrey Kaprin[1]

[1]*National Medical Research Radiological Center, Obninsk 249036, Russia;* [2]*Russian University of Transport, Moscow 127055, Russia*

We read with the great interest the brilliant review by Xiong *et al*. (2025), which explored cellular senescence investigations and the future clinical applications of senolytic therapies to address musculoskeletal disease [1]. Among the perspectives of senolytic and immune therapies in the context of senescence heterogeneity, the advanced breakthrough into age-related musculoskeletal disease interventions requires insights from another side of senescent interactions, as cell–cell communications.

Cellular senescence is currently recognized as a significant phenomenon involving cellular alterations that lead to the loss of normal regulation, initiation of cellular stasis, aging, and ultimately cell death [2]. Specific terms such as senescence, senolytics, senescence-associated secretory phenotype (SASP), inflammaging, and reversal of senescence have recently been added by the phenomenon of senescent drift induction in surrounding tissues, where senescent cells influence neighboring cells to become senescent as well [3,4].

Interestingly, the term "senescent drift" was first used in the context of fruit production and storage, which could provide us with some important insights. In fruit production, senescent drift refers to the gradual decline in quality and physiologic function of fruits as they age post-harvest. This process involves a series of biochemical and physical changes that degrade the texture, flavor, nutritional value, and overall appearance of the fruit. Initially, the term "senescent drift" for the apples storing was introduced in Imperial Botanical Conference 1924 in London by a British plant physiologist, Dr. Frederick Blackman [5]. As the animal cells in solid tissues, the apples produced metabolites, which is able to accelerate the fruit ripening and lead to their rotting [6]. The apple ripening model illustrates that not only does the rotting matter (analogous to "SASP"), but the entire storage process (analogous to "senescent drift") is important.

In the context of cellular senescence, the SASP phenotype is typically characterized by changes in cellular regulation, and could be played as a target for the senolytic therapy. However, senescence drift can be explained in terms of tissue-specific responses to the SASP of senescent cells. The proposed mechanism of senescent drift differs from the well-known SASP because senescent cells secrete a wide variety of pro-inflammatory signals that do not cause widespread senescence in tissues. The SASP cells produce a "shotgun" effect in all tissues, but spontaneous senescence induction in tissues could not appear. Therefore, the promotion of senescence in surrounding tissues cannot be explained by a wide secretory activity alone, but rather by secretion affinity, i.e., the special exosome phenotype or RNA-protein complexes that drive them to merge with target cells [4]. The secretion of an affinity-targeted secretome could be the underlying mechanism of senescent drift in tissues (Fig. 1).

Cellular senescence can drive fibrotic processes in various musculoskeletal tissues by secreting factors that promote fibroblast activation and ECM deposition [7]. In cartilaginous tissues senescent cells in joints can influence surrounding cells by SASP. In bone tissue, SASP factors can promote osteoclastogenesis, which leads to increased bone resorption and decreased bone density, characteristics of osteoporosis. Senescent cells in muscle tissue secrete factors that inhibit the proliferation and differentiation of satellite cells, contributing to the muscle wasting and weakness observed in sarcopenia. In intervertebral discs, senescent cells can stimulate the secretion of pro-inflammatory mediators and matrix metalloproteinases, leading to ECM degradation and promoting disc degeneration [7,8]. Therefore, one of the

Received July 2, 2025; accepted August 27, 2025
Correspondence: Ilya Klabukov, ilya.klabukov@gmail.com

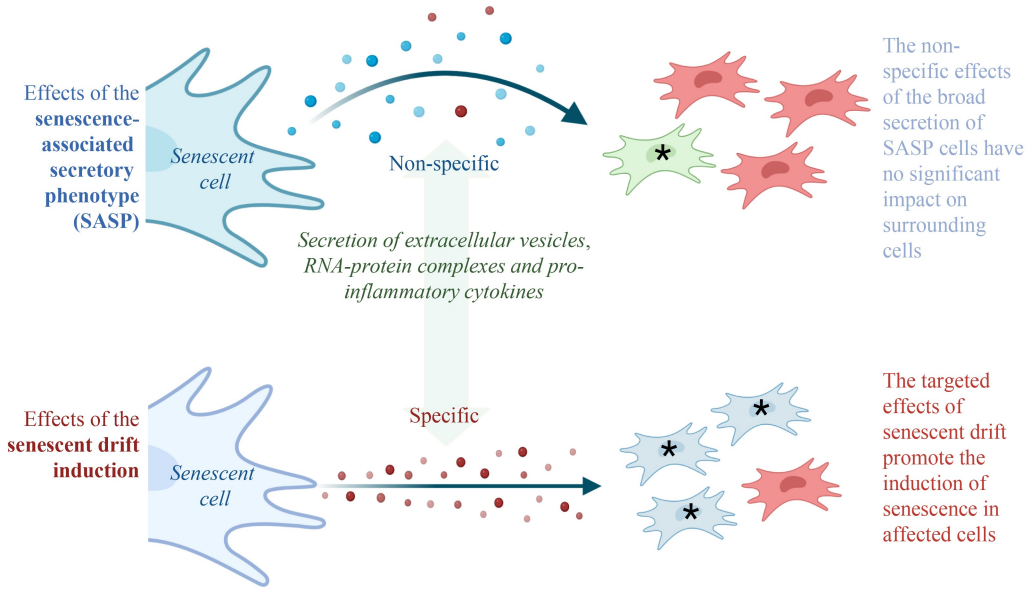

Fig. 1 Effects of SASP and the senescent drift induction for surrounding cells. Created with Biorender.com.

key targets of anti-senescent therapy could be to enhance the maintenance of cells against cellular senescence. This idea was only once mentioned in the review, but the epigenetic modifications are not disclosed in detail. Indeed, DNA demethylation or inhibition of histone deacetylases could potentially rejuvenate senescent cells or prevent their detrimental effects on surrounding tissues. The use of epigenetic drugs that modify DNA methylation or histone acetylation could be an innovative approach to modulate the SASP and potentially reverse or delay the onset of cellular senescence.

These effects are associated with epigenetic reprogramming without loss of cell identity, suggesting that controlled demethylation can reverse signs of aging [9]. Lu *et al.* showed that targeted demethylation can restore youthful function, even in aged neurons [10]; it was also shown that HDAC inhibition has conserved anti-aging effects across species [11]. Therefore, both DNA demethylation and HDAC inhibition have been shown to rejuvenate cells and tissues, restore function, and, in some cases, extend lifespan in experimental models. These findings provide solid scientific justification for proposing epigenetic modulation as a therapeutic target in aging.

We believe this nuanced point could be instrumental in advancing the understanding of not only cellular changes, but also changes in cell-to-cell communication. This tiny point could advance the future of senescence research and age-related disease treatments.

Compliance with ethics guidelines

Conflicts of interest Ilya Klabukov, Elizabeth Skornyakova, Daria Eygel, Denis Baranovskii, Peter Shegay, and Andrey Kaprin declare no conflict of interest, financial or otherwise.

This manuscript is a comment and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. Xiong J, Guo Q, Luo X. Cellular senescence in age-related musculoskeletal diseases. Front Med 2025; 19(3): 409–426
2. Roger L, Tomas F, Gire V. Mechanisms and regulation of cellular senescence. Int J Mol Sci 2021; 22(23): 13173
3. Sun W, Lv J, Guo S, Lv M. Cellular microenvironment: a key for tuning mesenchymal stem cell senescence. Front Cell Dev Biol 2023; 11: 1323678
4. Smirnova A, Yatsenko E, Baranovskii D, Klabukov I. Mesenchymal stem cell-derived extracellular vesicles in skin wound healing: the risk of senescent drift induction in secretome-based therapeutics. Mil Med Res 2023; 10(1): 60
5. Blackman FF. The biological problems of the cold storage of apples. In: Imperial Botanical Conference Proceedings. London, July 7–16, 1924. 18–20
6. Kidd F, West C. Physiology of Fruit. I. Changes in the respiratory activity of apples during their senescence at different temperatures. Proc R Soc Lond, B 1930; 106(742): 93–109
7. Falvino A, Gasperini B, Cariati I, Bonanni R, Chiavoghilefu A, Gasbarra E, Botta A, Tancredi V, Tarantino U. Cellular senescence: the driving force of musculoskeletal diseases. Biomedicines 2024; 12(9): 1948
8. Alqahtani S, Alqahtani T, Venkatesan K, Sivadasan D, Ahmed R, Sirag N, Elfadil H, Abdullah Mohamed H, Haseena TA, Elsayed Ahmed R, Muralidharan P, Paulsamy P. SASP modulation for cellular rejuvenation and tissue homeostasis: therapeutic strategies and molecular insights. Cells 2025; 14(8): 608
9. Abraira VE, Kuehn ED, Chirila AM, Springel MW, Toliver AA,

Zimmerman AL, Orefice LL, Boyle KA, Bai L, Song BJ, Bashista KA, O'Neill TG, Zhuo J, Tsan C, Hoynoski J, Rutlin M, Kus L, Niederkofler V, Watanabe M, Dymecki SM, Nelson SB, Heintz N, Hughes DI, Ginty DD. The cellular and synaptic architecture of the mechanosensory dorsal horn. Cell 2017; 168(1): 295–310.e19

10. Lu Y, Brommer B, Tian X, Krishnan A, Meer M, Wang C, Vera DL, Zeng Q, Yu D, Bonkowski MS, Yang JH, Zhou S, Hoffmann EM, Karg MM, Schultz MB, Kane AE, Davidsohn N, Korobkina E, Chwalek K, Rajman LA, Church GM, Hochedlinger K, Gladyshev VN, Horvath S, Levine ME, Gregory-Ksander MS, Ksander BR, He Z, Sinclair DA. Reprogramming to recover youthful epigenetic information and restore vision. Nature 2020; 588(7836): 124–129
11. Buck SA, Steinkellner T, Aslanoglou D, Villeneuve M, Bhatte SH, Childers VC, Rubin SA, De Miranda BR, O'Leary EI, Neureiter EG, Fogle KJ, Palladino MJ, Logan RW, Glausier JR, Fish KN, Lewis DA, Greenamyre JT, McCabe BD, Cheetham CEJ, Hnasko TS, Freyberg Z. Vesicular glutamate transporter modulates sex differences in dopamine neuron vulnerability to age-related neurodegeneration. Aging Cell 2021; 20(5): e13365