IJHSR
ijhighschoolresearch.org
REVIEW ARTICLE

Targeting Cellular Senescence: The Role of Collagen and Fibroblasts in Senotherapeutic Strategies

Youn-Jean Han

Ewha Girl's High School, 26 Jeongdong-gil, Jung-gu, Seoul 04517, Republic of Korea; younjeanhan@gmail.com

ABSTRACT: Cellular senescence contributes to organismal aging and age-related diseases through the irreversible cell-cycle arrest and a pro-inflammatory secretome, known as the senescence-associated secretory phenotype (SASP). Fibroblasts play an essential role in preserving the balance of the extracellular matrix (ECM) by producing and reorganizing collagen and other structural proteins. As the body ages, however, these cells gradually enter a senescent state and begin releasing matrix metalloproteinases (MMPs) and inflammatory cytokines, which can break down collagen and alter normal tissue structure. Dysregulation of collagen metabolism, such as reduced synthesis and excessive degradation, underlies many age-related pathologies, ranging from skin wrinkles to organ fibrosis. This review discusses the mechanisms of fibroblast senescence and collagen aging, and surveys "senotherapeutic" strategies, senolytics, senomorphics, fibroblast reprogramming, and biomaterials that target these processes. In addition, it summarizes recent studies of interventions targeting senescent fibroblasts and collagen. It compares aging-associated collagen changes across tissues, emphasizing applications in skin regeneration, orthopedics, cardiovascular repair, and fibrosis.

KEYWORDS: Medical and Health Sciences, Cell Biology, Fibroblast Senescence, Collagen Remodeling, Senotherapeutics.

Introduction

Aging is a multifactorial and inevitable biological process characterized by a gradual decline in the structural integrity and function of tissues across organ systems. One of the most recognized cellular hallmarks of aging is cellular senescence, a state of permanent growth arrest in which cells lose the ability to divide but remain metabolically active.[1] Initially, cellular senescence serves beneficial roles, such as preventing tumorigenesis and promoting wound healing.[2] Over time, however, the chronic accumulation of senescent cells (SnCs) drives persistent inflammation, fibrosis, and functional decline across multiple organs.[3] This paradox has made SnCs a major therapeutic target in modern aging research.[2]

Among the various cell types prone to senescence, fibroblasts play a particularly central role because they maintain the ECM, a network of proteins that gives tissues their structure and strength.[4] With age, fibroblasts lose their normal regenerative capacity and develop SASP, meaning they start releasing many inflammatory molecules that can affect nearby cells.[2] Senescent fibroblasts begin secreting proinflammatory cytokines and matrix-degrading proteases that cleave collagen, the most abundant protein in the ECM.[4] As the disruption of collagen homeostasis continues with age, tissues gradually lose their structural strength, becoming more lax and slower to heal, while developing a pro-fibrotic environment in many organs. Consequently, fibroblast senescence and collagen imbalance form a pathological nexus underlying the link between molecular aging and overt tissue degeneration.[5]

This review aims to highlight the close relationship between fibroblast senescence and collagen remodeling, emphasizing how these processes together drive tissue degeneration. It summarizes the mechanisms by which senescent fibroblasts alter the collagenous microenvironment. The review cfurther discusses senotherapeutic interventions, including senolytic and senomorphic agents, fibroblast rejuvenation techniques, and collagen-based biomaterials, aimed at restoring tissue integrity. Finally, it discusses how these approaches extend beyond the skin to other organs and outlines the current limitations and translational challenges that must be overcome to realize senescence-targeted regenerative medicine.

Discussion

Mechanism: From SnCs and SASP to Collagen Breakdown:

SnCs are characterized by an irreversible cell-cycle arrest accompanied by an active secretory phenotype.[6] Senescence can be triggered by telomere shortening, DNA damage, oncogenic signals, or other stresses that activate tumor-suppressor pathways (p53/$p21^{CIP1}$ and $p^{16INK4a/Rb}$), which are key proteins that enforce cell-cycle arrest and prevent damaged cells from dividing, enforcing permanent growth arrest.[7] SnCs resist apoptosis and instead secrete a complex SASP. Key SASP factors include pro-inflammatory cytokines such as IL-6, IL-1β, and IL-8, as well as chemokines (CXCL family), growth factors (TGF-β and PDGF), and proteases (MMP-1, MMP-3, and MMP-9).[8] SASP factors can act on nearby cells through both autocrine and paracrine signaling, causing them to enter a senescent state as well. Over time, this process contributes to ongoing tissue remodeling and inflammation. As this chronic SASP persists, it promotes a low-grade inflammatory environment that leads to fibrosis, disrupts stem cell function, and accelerates tissue aging.[6] Recent single-cell studies comparing active and inactive keloid scars have shown that certain fibroblast groups involved in inflammation and blood vessel formation are much more

DOI: 10.36838/IJHSR86.55

abundant in active lesions. This finding suggests that fibroblast diversity and ongoing inflammation may both contribute to the abnormal collagen remodeling seen in keloids.[9] Importantly, SASP proteases directly target the ECM: secretion of MMPs by SnCs cleaves collagen and other matrix components, leading to structural breakdown of tissues. Dermal fibroblasts, for example, produce a SASP that is especially rich in MMP-2, MMP-9, and inflammatory cytokines such as IL-6 and IL-8, which directly weaken the collagen scaffold of the skin.[5,10] As shown in Figure 1, senescent dermal fibroblasts in aged skin secrete MMPs and pro-inflammatory cytokines that fragment collagen fibers and perpetuate local inflammation.

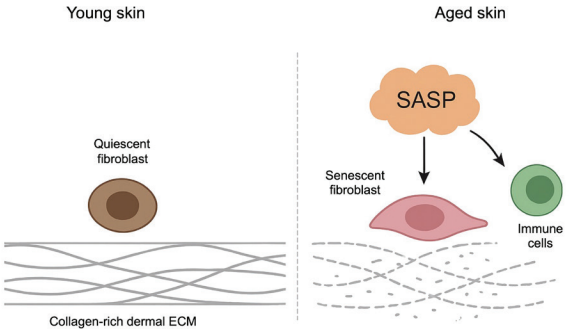

Figure 1: Comparison of fibroblast activity and collagen structure in young and aged Skin. In young skin (left), quiescent fibroblasts (brown) maintain a collagen-rich dermal ECM. Fibroblasts in aged skin (right) enter a senescent state (pink) and release SASP factors that gradually weaken and fragment the collagen network (gray dashed fibers). This figure highlights how senescent fibroblasts contribute to collagen fragmentation and local inflammation, illustrating the central mechanism of skin aging. It visually compares young and aged skin to emphasize how fibroblast senescence leads to ECM damage.

This loss of collagen integrity represents a central mechanism of skin aging. Collagen fragmentation further disrupts cell-matrix signaling. Studies have shown that collagen fragments trigger aberrant responses in fibroblasts, including upregulation of additional MMPs and suppression of new collagen synthesis.[11] In photoaged skin, ultraviolet (UV)-induced collagen breakdown leads to a senescencelike phenotype in fibroblasts, reinforcing this feedback loop of damage. Conversely, age-related alterations in collagen mechanics can themselves promote fibroblast senescence. A stiffened collagen matrix increases integrin signaling, the way cells sense and respond to the stiffness of their surroundings, which then triggers $p^{16INK4A}$ expression in fibroblasts. In this way, deterioration of the collagenous ECM contributes to SnCs accumulation, while SnCs in turn accelerate collagen degradation, forming a vicious cycle of aging.[12,13] Conversely, recent studies demonstrate that upregulation of HSP47 in dermal fibroblasts enhances type I collagen secretion and restores matrix homeostasis, highlighting the potential of molecular chaperone–based approaches to counteract fibroblast senescence.[14]

Therapeutic Strategies Targeting Senescent Fibroblasts and Collagen:

Therapeutic approaches to mitigate fibroblast senescence and its impact on collagen homeostasis can be broadly categorized into four mechanistic groups: senolytics, senomorphics, fibroblast rejuvenation strategies, and collagen-based biomaterials. Senolytic drugs (compounds that specifically eliminate SnCs) have shown promising results in restoring collagen production. In contrast, senomorphic agents (drugs that calm harmful secretions from SnCs without killing them) help reduce chronic inflammation and tissue damage.[15] Senolytics selectively eliminate SnCs, whereas senomorphics suppress SASP and other deleterious SnC activities without inducing cell death. Fibroblast rejuvenation techniques, such as transient reprogramming or exposure to youthful paracrine factors, aim to restore aged fibroblasts to a more youthful state. Finally, collagen-based biomaterials can directly counteract collagen loss while modulating fibroblast-ECM interactions to promote tissue integrity. Table 1 summarizes recent senotherapeutic interventions (2020–2025) targeting senescent fibroblasts, including each agent's mechanism, experimental model, and major outcomes related to senescence and collagen regulation. To provide a conceptual overview, Figure 2 schematically illustrates these four therapeutic categories, highlighting how each strategy acts on senescent fibroblasts and collagen remodeling.

Table 1: Recent senotherapeutic interventions (2020–2025) targeting fibroblasts. The listed studies illustrate how different senolytic and senomorphic agents alleviate fibroblast senescence, reduce SASP factors, and promote collagen regeneration across experimental models.

Agent	Target / Mechanism	Experimental Model	Outcomes	References
Dasatinib + Quercetin	Multi-kinase inhibitor + antioxidant	Radiation-induced senescent human dermal	Selective elimination of senescent fibroblasts; decreased $p16^{INK4A}$	[16]
		fibroblasts; aged mouse skin ulcer model	and SASP factors; increased Ki67 expression and improved ulcer healing.	
ABT-263 (Navitoclax)	BCL-2/BCL-xL inhibitor (BH3 mimetic)	Aged mouse skin (24-month-old; topical application)	Selective ablation of $p16^{+}$ SnCs; reduced p16/p21 and SA-β-gal; increased collagen gene expression and accelerated wound closure	[17]
FOXO4-DRI peptide	Disrupts FOXO4–p53 interaction	Senescent human keloid fibroblasts and tissue organ culture	Induced apoptosis of $p16^{+}$ senescent fibroblasts; alleviated collagen fibrosis in keloid tissue	[18]
Fisetin	Polyphenol flavonoid (senolytic)	UV-induced senescent human fibroblasts; aged human skin grafts in mice	Selective removal of SnCs; reduced IL-6 and MMPs; increased type I collagen content and improved dermal matrix organization	[19]

Rapamycin	mTOR inhibitor (senomorphic)	UVA-irradiated human dermal fibroblasts	Reduced SA-β-gal+ cells and SASP (MMP-1 and MMP-3); increased type I collagen and autophagy activation	[20]
Valsartan + Metformin	AT1 receptor antagonist + AMPK activator (metabolic modulator)	Senescent human dermal fibroblasts (thermoresponsive hydrogel delivery)	Partial reversal of cellular phenotype; increased collagen production and pro-collagen gene expression	[21]
BTSA1	BAX activator (pro-apoptotic small molecule)	Mouse model of bleomycin-induced pulmonary fibrosis	Selective apoptosis of senescent myofibroblasts; decreased fibrosis and collagen deposition; improved lung function	[22]
R406	SYK kinase inhibitor (HSP90 pathway disruptor)	Senescent human dermal fibroblasts	Induced apoptosis of SnCs; decreased viability of senescent but not healthy fibroblasts	[23]

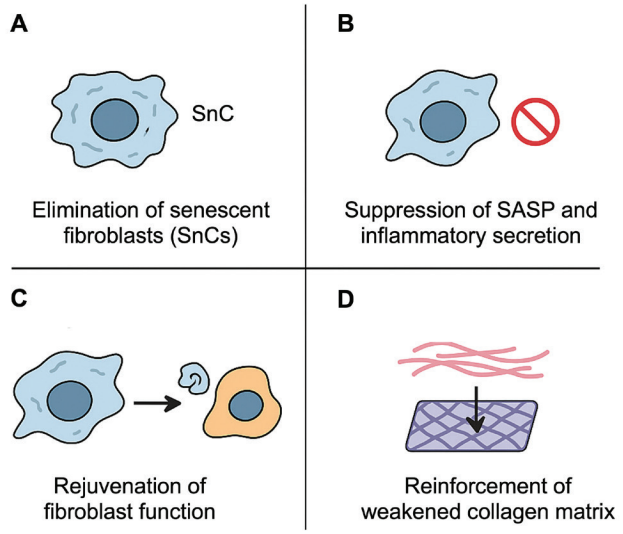

Figure 2: Schematic summary of four main strategies that reduce fibroblast senescence and improve collagen remodeling. This figure organizes the main therapeutic approaches into four categories, showing how each supports fibroblast rejuvenation and collagen repair. These include (A) senolytic agents, (B) senomorphic compounds, (C) methods that rejuvenate fibroblast function, and (D) collagen-based biomaterials designed to restore tissue integrity. Together, they provide a clear overview of how different approaches can cooperate to rebuild healthy tissues.

Senolytic Therapies:

Senolytic therapies are based on the principle that SnCs rely on specific anti-apoptotic and survival signaling networks, known as SnC anti-apoptotic pathways (SCAPs), to resist programmed cell death. By pharmacologically blocking these pathways, senolytics trigger apoptosis in SnCs while sparing normal, proliferative, or quiescent cells.[24] For instance, the well-known senolytic combination dasatinib and quercetin (D+Q) targets multiple kinases and oxidative stress pathways to induce apoptosis in SnCs. In dermal fibroblasts, this treatment reduces SASP cytokines such as IL-6 and MMPs while restoring collagen synthesis.[16,25] Similar outcomes have been reported for the BH3 mimetic navitoclax, which inhibits BCL-2/BCL-xL to selectively clear senescent fibroblasts and enhance collagen remodeling.[17,26] Other senolytics, including FOXO4-DRI, fisetin, and BTSA1, act through different apoptotic checkpoints but share the same goal, removing SnCs to rejuvenate the surrounding tissue microenvironment.[18,19,22]

Senomorphic Therapies:

Senomorphic therapies, often called senostatics, are designed to reduce the negative impact of SnCs without removing them. They work by limiting the SASP response through the regulation of major signaling pathways related to inflammation and aging, including NF-κB, mTOR, and JAK/STAT.[27] By dampening SASP activity, senomorphics can reduce chronic inflammation and prevent tissue damage caused by accumulated SnCs. A well-studied example is rapamycin, an mTOR inhibitor that lowers SASP factors and helps restore ECM balance.[20] Other compounds, such as JAK1/2 inhibitors or metabolic regulators like metformin, similarly adjust SASP transcription and limit collagen degradation. By maintaining the viability of fibroblasts while normalizing their secretory profile, senomorphic agents help control the harmful activity of SnCs and support normal tissue function without removing the cells.

Fibroblast Rejuvenation:

Fibroblast rejuvenation strategies aim to restore the normal function of aging fibroblasts so that they can once again support tissue repair and maintenance. These methods often focus on reprogramming or adjusting aged fibroblasts to recover healthier epigenetic and metabolic patterns. As a result, the cells may regain their ability to divide, produce collagen, and maintain the ECM. Recent findings provide evidence for this idea. In one study, researchers partially reprogrammed aged fibroblasts on micropatterned surfaces and then allowed them to re-differentiate within a three-dimensional collagen matrix. The resulting fibroblasts showed fewer signs of DNA damage, better cytoskeletal structure, and greater ECM production compared to untreated cells.[28] Likewise, transient expression of Yamanaka factors in middle-aged human fibroblasts reversed several aging markers. These cells regained a more youthful transcriptomic profile, increased collagen expression, and improved migratory capacity.[29] In addition, treatment with cold atmospheric plasma (a non-thermal ionized gas) was found to protect dermal fibroblasts from oxidative stress and delay their senescence, ultimately preventing UV-induced wrinkle formation.[30] Taken together, these results indicate that carefully regulating cellular reprogramming and the surrounding microenvironment can help revive fibroblast function and promote tissue regeneration.

Collagen-Based Biomaterials:

Collagen-based biomaterials are engineered scaffolds composed of collagen designed to mimic the natural cellular environment and facilitate tissue regeneration, repair, and

DOI: 10.36838/IJHSR86.55

functional recovery. Because collagen possesses excellent biocompatibility and intrinsic cell-binding sites, collagen-based materials form a three-dimensional framework that supports cellular attachment, migration, and proliferation.[31] In aging skin and chronic wounds, collagen-based sponges, dressings, and hydrogels act as temporary scaffolds that facilitate fibroblast migration while regulating the retention and release of growth factors. Furthermore, these collagen matrices can modulate fibroblast activity. Porous collagen scaffolds seeded with fibroblasts or mesenchymal stem cells have been demonstrated to promote dermal regeneration and attenuate scar formation.[32] Recently, researchers have developed "smart" collagen biomaterials functionalized with bioactive molecules. For example, collagen hydrogels can be loaded with senolytic or anti-inflammatory drugs to remove SnCs or suppress SASP at the implantation site locally.[33] In clinical dermatology, collagen remodeling and rejuvenation are also pursued through practical strategies, such as combining radiofrequency (RF) energy devices with collagen-stimulating injectables like poly-L-lactic acid fillers, which have demonstrated efficacy in improving skin elasticity and dermal structure.[34] Likewise, a clinical study using biocompatible magnesium microneedle patches showed measurable wrinkle reduction and increased dermal thickness, suggesting that minimally invasive mechanical stimulation can activate dermal fibroblasts and promote collagen regeneration.[35] Similarly, a dissolvable microstructure patch made of crosslinked hyaluronic acid has been shown to improve skin hydration and reduce fine wrinkles without irritation significantly.[36]

Implications for Other Organs:

While the preceding sections focused on dermal fibroblasts and collagen remodeling in the skin, similar senescence–collagen interactions have been identified across multiple organs. In many tissues, fibroblast dysfunction contributes to fibrosis, loss of elasticity, and age-related functional decline.

Heart: In the aging heart, the accumulation of senescent fibroblasts together with disruptions in collagen remodeling plays a central role in driving myocardial stiffness and the subsequent decline in cardiac performance. Unlike the skin, where collagen levels typically decrease with age, the aging heart shows an opposite trend as excess collagen accumulates around cardiomyocytes, leading to interstitial fibrosis and reduced tissue compliance.[37] Following myocardial infarction (MI), activated fibroblasts deposit collagens I and III to stabilize the injured area.[38] Although fibroblast activation initially serves a protective role after cardiac injury, its persistent stimulation and the onset of senescence eventually lead to excessive collagen crosslinking and stiff scar formation that impairs contractility.[39] This maladaptive fibrosis is a hallmark of diastolic heart failure. Senescent fibroblasts worsen cardiac dysfunction by secreting pro-inflammatory SASP components and driving excessive ECM deposition. In aged mouse models, the targeted removal of these SnCs has been reported to lessen fibrosis and myocardial hypertrophy, ultimately improving diastolic performance. Senolytic agents that inhibit anti-apoptotic proteins, including BCL-2 and BCL-xL, have further been shown to enhance both ejection fraction and electrical signaling in preclinical studies.[40] At the same time, progress in biomaterial-based therapies is promising, as acellular collagen patches and injectable hydrogels not only reinforce the injured myocardium structurally but also influence fibroblast activity in ways that promote tissue repair. Type I collagen-based scaffolds, for instance, have been shown to reduce scar size and adverse remodeling after MI.[41] Beyond cardiac tissue, fibrotic skin disorders such as keloids exhibit excessive fibroblast activation and collagen deposition, leading to pathological ECM accumulation. Notably, a recent three-dimensional keloid spheroid model demonstrated that interactions between fibroblasts and the ECM can influence drug responsiveness, suggesting its value as a platform for developing personalized anti-fibrotic therapies.[42]

Lung: Fibroblast senescence is also a central mechanism in pulmonary fibrosis and age-related lung decline. In idiopathic pulmonary fibrosis (IPF), senescent myofibroblasts persist and secrete excessive ECM, driving progressive scarring.[22,43] Their SASP promotes chronic inflammation and secondary senescence, creating a self-sustaining disease cycle.[44] Recent work has shown encouraging results with senescence-targeted interventions. Dasatinib plus quercetin reduced fibrosis in bleomycininduced models,[45] and early clinical studies in IPF patients indicate feasibility and potential biomarker improvements.[46] Beyond drug-based therapies, bioengineering approaches seek to normalize the microenvironment. Soft or degradable scaffolds that modulate ECM stiffness can suppress fibroblast activation and encourage regeneration. Thus, a combined strategy, first eliminating SnCs, then rebuilding a healthy ECM, may be the most effective path toward restoring lung function.

Liver: The liver provides a clear example of how cellular senescence can exert both beneficial and detrimental effects depending on the physiological context. During acute injury, hepatic stellate cells (HSCs) activate to deposit collagen but later enter senescence, which helps halt further fibrosis. These senescent HSCs also release enzymes and immune signals that aid scar resolution and attract natural killer cells to clear excess tissue.[47] However, if these cells are eliminated too early, recovery may be impaired since they also secrete regenerative cytokines such as IL-6.[48] In contrast, in chronic liver disease, senescent HSCs and hepatocytes persist, maintaining inflammation and promoting fibrosis. Senescent hepatocytes accumulate in advanced fatty liver disease, where their SASP contributes to both fibrogenesis and carcinogenesis.[49]

Recent transcriptomic analyses identified a senescent hepatocyte gene signature (SHGS) in metabolic dysfunction-associated steatotic liver disease. Removing SHGS-positive hepatocytes improved liver function and reduced fibrosis in obese mice.[50] At the same time, biomaterial platforms such as decellularized liver ECM scaffolds offer structural cues that may support regeneration once fibrosis subsides.[51] Taken together, these observations emphasize that the effects of senescence are highly context-dependent, which reinforces the importance of developing interventions that are both selective and time-sensitive.

Other Organs: Comparable fibroblast–collagen interactions occur in other aging organs. In the kidney, senescent fibroblast-like cells accumulate after chronic injury, promoting interstitial fibrosis and renal dysfunction. Senolytic treatments have reduced fibrosis and accelerated repair in experimental models.[52–54] In osteoarthritic joints, senescent chondrocytes and synoviocytes degrade collagen and perpetuate inflammation; removing these cells decreased cartilage loss and pain in preclinical studies, inspiring early intra-articular senolytic trials.[55,56] In the eye, senescent corneal and conjunctivalfibroblasts contribute to scarring after injury or surgery, whereas targeting oxidative stress or TGF-β pathways enhances regeneration.[57,58] In bone marrow, senescent stromal cells promote fibrosis and impair hematopoiesis, but inhibition of inflammatory mediators such as NLRP3 or S100A9 can counteract these effects.[59] Taken together, these studies highlight a unifying mechanism in which senescent fibroblasts and disrupted collagen homeostasis drive fibrosis and functional decline across diverse organs. Combining senolytic strategies with regenerative biomaterials could therefore represent a versatile therapeutic avenue for restoring tissue function beyond the skin.

Limitations:

Although significant progress has been made, several biological and practical challenges must still be overcome before fibroblast-directed senescence therapies can be safely implemented in clinical settings.

Heterogeneity:

Senescent fibroblasts are highly heterogeneous and lack a universal marker that can reliably distinguish them from normal or transiently arrested cells.[60] Moreover, differentiating harmful, chronically senescent fibroblasts from transient, beneficial senescence that supports processes such as wound healing is complex.[61] This heterogeneity complicates efforts to achieve selective targeting, since current senolytic agents may inadvertently eliminate fibroblasts that serve transient but beneficial functions during tissue repair. To overcome this limitation, the development of more refined biomarkers and lineage-tracing approaches will be crucial for enabling accurate and context-specific therapeutic interventions.

Off-Target and Systemic Considerations:

Many senolytic and senomorphic compounds have broad systemic actions that may affect healthy cells. For instance, the BCL-2 family inhibitor navitoclax can also harm proliferating cells, leading to thrombocytopenia through platelet depletion.[62] To precisely target senescent fibroblasts in specific organs, like the skin, lungs, or heart, future treatments will likely depend on smart delivery systems, such as nanoparticles, antibody–drug conjugates, or prodrugs that become active only within fibrotic tissues.[63] In real-world applications, one of the biggest challenges in developing senotherapeutic treatments is finding the right balance, making them strong enough to work effectively, yet gentle enough to avoid unwanted toxicity.

Immune and Microenvironment Interactions:

The interactions among SnCs, immune components, and the surrounding ECM further contribute to the multifaceted nature of tissue remodeling. The elimination of SnCs can provoke an acute immune response, characterized by the recruitment of macrophages and natural killer cells that help clear residual cellular debris.[64] In aged individuals, the inflammatory response to senolytic therapy may become unpredictable. Moreover, senescent fibroblasts often reside in stiff, fibrotic ECM regions. Simply eliminating these cells without addressing the altered microenvironment may lead to recurrence of senescence or continued fibrosis.[65] Optimizing treatment timing and dosing, perhaps by combining senolytics with ECM-modifying or anti-fibrotic agents, could help maintain immune balance and promote true regeneration.

Biomaterial and Delivery:

Collagen scaffolds and other biomaterials hold promise as localized delivery systems, but they also present design challenges. If a scaffold is too stiff or excessively crosslinked, it may hinder fibroblast migration or even provoke fibrosis instead of repair.[66] Moreover, biomaterials designed to deliver therapeutic agents should provide stable release kinetics and precise targeting of senescent microenvironments within tissues.[33] Future biomaterial platforms will need to integrate spatiotemporal control, releasing therapeutic factors only when and where SnCs are detected.

Future Perspectives

Going forward, research efforts should focus on addressing the existing limitations of senescencetargeted therapies by enhancing both their biological specificity and translational potential. In addition, extrinsic aging factors, such as photoaging, deserve attention, as they accelerate fibroblast senescence and collagen breakdown in the skin. For example, chronic UV exposure triggers the TGFβ/Smad3 signaling pathway, which elevates MMP activity and increases reactive oxygen species, thereby accelerating collagen breakdown and skin aging. Moreover, senescent keratinocytes in photoaged skin may influence nearby fibroblasts through paracrine signaling, potentially amplifying tissue aging.[67] One key direction is to identify reliable biomarkers that can distinguish harmful, chronically senescent fibroblasts from transient, beneficial ones in living tissues. In parallel, scientists are developing targeted delivery systems such as antibody–drug conjugates and ligand-modified nanoparticles that can recognize unique surface proteins on senescent fibroblasts and deliver drugs directly to these cells.[68] Another important step will be to design combination strategies that integrate multiple therapeutic approaches. For instance, pairing senolytics with pro-regenerative factors like growth factors, ECM–modifying enzymes, or partial reprogramming signals could both eliminate SnCs and stimulate the regeneration of healthy fibroblasts. Long-term studies will also be essential to understand how extensive clearance of SnCs affects overall tissue stability, immune function, and even cancer risk.[69] Ultimately, the success of senescence-based interventions will depend on patientspecific factors. Identifying

DOI: 10.36838/IJHSR86.55

which individuals or tissues carry a particularly high burden of senescent fibroblasts will help tailor treatments more effectively. While the path forward is technically demanding, the progress so far suggests that targeting fibroblast senescence by combining with precise delivery and personalized design could become a transformative strategy for rejuvenating aged tissues in the future.

Conclusion

Fibroblast senescence and collagen remodeling are the key contributors to tissue aging and degeneration. In the skin, these changes appear as thinning, wrinkles, and slower wound healing. In other organs, they are linked to fibrosis and reduced elasticity. Targeting senescent fibroblasts— through selective removal, suppression of the SASP, or cellular rejuvenation—may help lower inflammation and restore more balanced collagen turnover. At the same time, recent progress in biomaterial design has introduced new ways to strengthen or replace the ECM, providing a supportive setting for tissue repair. Promising studies in animals show improved wound healing in aged skin and reduced fibrosis in organs such as the lung and heart, suggesting real therapeutic potential. Still, moving these strategies into clinical use will require careful control. Treatments must avoid unwanted effects, account for the differences among tissues, and remain safe over time. Looking ahead, combining senolytic drugs with collagen-based scaffolds or using biomaterials that release healing signals may lead to longer-lasting outcomes. In summary, tackling fibroblast senescence and collagen imbalance could become a key approach for rejuvenating aging tissues. By restoring both structure and function, this line of research has the potential to support healthy tissue regeneration.

Acknowledgments

The author gratefully acknowledges Prof. Dong Hun Lee at the Seoul National University College of Medicine for his valuable guidance and insightful discussions during the preparation of this manuscript.

References

1. López-Otín, C.; Blasco, M. A.; Partridge, L.; Serrano, M.; Kroemer, G. The Hallmarks of Aging. *Cell* **2013**, *153* (6), 1194–1217. https://doi.org/10.1016/j.cell.2013.05.039.
2. Kumari, R.; Jat, P. Mechanisms of Cellular Senescence: Cell Cycle Arrest and Senescence Associated Secretory Phenotype. *Front Cell Dev Biol* **2021**, *9*. https://doi.org/10.3389/fcell.2021.645593.
3. O'Reilly, S.; Markiewicz, E.; Idowu, O. C. Aging, Senescence, and Cutaneous Wound Healing—a Complex Relationship. *Front Immunol* **2024**, *15*. https://doi.org/10.3389/fimmu.2024.1429716.
4. Quan, T.; Fisher, G. J. Role of Age-Associated Alterations of the Dermal Extracellular Matrix Microenvironment in Human Skin Aging: A Mini-Review. *Gerontology* **2015**, *61* (5), 427–434. https://doi.org/10.1159/000371708.
5. Zhang, J.; Yu, H.; Man, M.; Hu, L. Aging in the Dermis: Fibroblast Senescence and Its Significance. *Aging Cell* **2024**, *23* (2). https://doi.org/10.1111/acel.14054.
6. Thompson, E. L.; Pitcher, L. E.; Niedernhofer, L. J.; Robbins, P. D. Targeting Cellular Senescence with Senotherapeutics: Development of New Approaches for Skin Care. *Plast Reconstr Surg* **2022**, *150*, 12S-19S. https://doi.org/10.1097/PRS.0000000000009668.
7. Kita, A.; Yamamoto, S.; Saito, Y.; Chikenji, T. S. Cellular Senescence and Wound Healing in Aged and Diabetic Skin. *Front Physiol* **2024**, *15*. https://doi.org/10.3389/fphys.2024.1344116.
8. Chen, W.; Kang, J.; Xia, J.; Li, Y.; Yang, B.; Chen, B.; Sun, W.; Song, X.; Xiang, W.; Wang, X.; Wang, F.; Wan, Y.; Bi, Z. P53-Related Apoptosis Resistance and Tumor Suppression Activity in UVB-Induced Premature Senescent Human Skin Fibroblasts. *Int J Mol Med* **2008**, *21* (5), 645–653.
9. Oh, S.; Yeo, E.; Shim, J.; Noh, H.; Park, J.; Lee, K.; Kim, S.; Lee, D.; Lee, J. H. Revealing the Pathogenesis of Keloids Based on the Status: Active vs Inactive. *Exp Dermatol* **2024**, *33* (5). https://doi.org/10.1111/exd.15088.
10. Wang, A. S.; Dreesen, O. Biomarkers of Cellular Senescence and Skin Aging. *Front Genet* **2018**, *9*. https://doi.org/10.3389/fgene.2018.00247.
11. Quan, T.; Little, E.; Quan, H.; Qin, Z.; Voorhees, J. J.; Fisher, G. J. Elevated Matrix Metalloproteinases and Collagen Fragmentation in Photodamaged Human Skin: Impact of Altered Extracellular Matrix Microenvironment on Dermal Fibroblast Function. *Journal of Investigative Dermatology* **2013**, *133* (5), 1362–1366. https://doi.org/10.1038/jid.2012.509.
12. Fisher, G. J.; Quan, T.; Purohit, T.; Shao, Y.; Cho, M. K.; He, T.; Varani, J.; Kang, S.; Voorhees, J. J. Collagen Fragmentation Promotes Oxidative Stress and Elevates Matrix Metalloproteinase-1 in Fibroblasts in Aged Human Skin. *Am J Pathol* **2009**, *174* (1), 101–114. https://doi.org/10.2353/ajpath.2009.080599.
13. Howes, A. M.; Dea, N. C.; Ghosh, D.; Krishna, K.; Wang, Y.; Li, Y.; Morrison, B.; Toussaint, K. C.; Dawson, M. R. Fibroblast Senescence-Associated Extracellular Matrix Promotes Heterogeneous Lung Niche. *APL Bioeng* **2024**, *8* (2). https://doi.org/10.1063/5.0204393.
14. Ham, S. M.; Song, M. J.; Yoon, H.-S.; Lee, D. H.; Chung, J. H.; Lee, S.-T. SPARC Is Highly Expressed in Young Skin and Promotes Extracellular Matrix Integrity in Fibroblasts via the TGF-β Signaling Pathway. *Int J Mol Sci* **2023**, *24* (15), 12179. https://doi.org/10.3390/ijms241512179.
15. Nan, L.; Guo, P.; Hui, W.; Xia, F.; Yi, C. Recent Advances in Dermal Fibroblast Senescence and Skin Aging: Unraveling Mechanisms and Pioneering Therapeutic Strategies. *Front Pharmacol* **2025**, *16*. https://doi.org/10.3389/fphar.2025.1592596.
16. Wang, H.; Wang, Z.; Huang, Y.; Zhou, Y.; Sheng, X.; Jiang, Q.; Wang, Y.; Luo, P.; Luo, M.; Shi, C. Senolytics (DQ) Mitigates Radiation Ulcers by Removing Senescent Cells. *Front Oncol* **2020**, *9*. https://doi.org/10.3389/fonc.2019.01576.
17. Shvedova, M.; Thanapaul, R. J. R. S.; Ha, J.; Dhillon, J.; Shin, G. H.; Crouch, J.; Gower, A. C.; Gritli, S.; Roh, D. S. Topical ABT-263 Treatment Reduces Aged Skin Senescence and Improves Subsequent Wound Healing. *Aging* **2025**, *17* (1), 16–32. https://doi.org/10.18632/aging.206165.
18. Kong, Y.-X.; Li, Z.-S.; Liu, Y.-B.; Pan, B.; Fu, X.; Xiao, R.; Yan, L. FOXO4-DRI Induces Keloid Senescent Fibroblast Apoptosis by Promoting Nuclear Exclusion of Upregulated P53-Serine 15 Phosphorylation. *Commun Biol* **2025**, *8* (1), 299. https://doi.org/10.1038/s42003-025-07738-0.
19. Takaya, K.; Asou, T.; Kishi, K. Fisetin, a Potential Skin Rejuvenation Drug That Eliminates Senescent Cells in the Dermis. *Biogerontology* **2024**, *25* (1), 161–175. https://doi.org/10.1007/s10522-023-10064-9.
20. Bai, G.-L.; Wang, P.; Huang, X.; Wang, Z.-Y.; Cao, D.; Liu, C.; Liu, Y.-Y.; Li, R.-L.; Chen, A.-J. Rapamycin Protects Skin Fibroblasts From UVA-Induced Photoaging by Inhibition of P53 and

Phosphorylated HSP27. *Front Cell Dev Biol* **2021**, *9*. https://doi.org/10.3389/fcell.2021.633331.
21. Kuhn, P. M.; Chen, S.; Venkatraman, A.; Abadir, P. M.; Walston, J. D.; Kokkoli, E. Co-Delivery of Valsartan and Metformin from a Thermosensitive Hydrogel-Nanoparticle System Promotes Collagen Production in Proliferating and Senescent Primary Human Dermal Fibroblasts. *Biomacromolecules* **2024**, *25* (9), 5702–5717. https://doi.org/10.1021/acs.biomac.3c01461.
22. Shen, M.; Fu, J.; Zhang, Y.; Chang, Y.; Li, X.; Cheng, H.; Qiu, Y.; Shao, M.; Han, Y.; Zhou, Y.; Luo, Z. A Novel Senolytic Drug for Pulmonary Fibrosis: BTSA1 Targets Apoptosis of Senescent Myofibroblasts by Activating BAX. *Aging Cell* **2024**, *23* (9). https://doi.org/10.1111/acel.14229.
23. Cho, H.-J.; Yang, E. J.; Park, J. T.; Kim, J.-R.; Kim, E.-C.; Jung, K.-J.; Park, S. C.; Lee, Y.-S. Identification of SYK Inhibitor, R406 as a Novel Senolytic Agent. *Aging* **2020**, *12* (9), 8221–8240. https://doi.org/10.18632/aging.103135.
24. Kirkland, J. L.; Tchkonia, T. Senolytic Drugs: From Discovery to Translation. *J Intern Med* **2020**, *288* (5), 518–536. https://doi.org/10.1111/joim.13141.
25. Takaya, K.; Kishi, K. Combined Dasatinib and Quercetin Treatment Contributes to Skin Rejuvenation through Selective Elimination of Senescent Cells in Vitro and in Vivo. *Biogerontology* **2024**, *25* (4), 691–704. https://doi.org/10.1007/s10522-024-10103-z.
26. Chang, J.; Wang, Y.; Shao, L.; Laberge, R.-M.; Demaria, M.; Campisi, J.; Janakiraman, K.; Sharpless, N. E.; Ding, S.; Feng, W.; Luo, Y.; Wang, X.; Aykin-Burns, N.; Krager, K.; Ponnappan, U.; Hauer-Jensen, M.; Meng, A.; Zhou, D. Clearance of Senescent Cells by ABT263 Rejuvenates Aged Hematopoietic Stem Cells in Mice. *Nat Med* **2016**, *22* (1), 78–83. https://doi.org/10.1038/nm.4010.
27. Imb, M.; Véghelyi, Z.; Maurer, M.; Kühnel, H. Exploring Senolytic and Senomorphic Properties of Medicinal Plants for Anti-Aging Therapies. *Int J Mol Sci* **2024**, *25* (19), 10419. https://doi.org/10.3390/ijms251910419.
28. Roy, B.; Yuan, L.; Lee, Y.; Bharti, A.; Mitra, A.; Shivashankar, G. V. Fibroblast Rejuvenation by Mechanical Reprogramming and Redifferentiation. *Proceedings of the National Academy of Sciences* **2020**, *117* (19), 10131–10141. https://doi.org/10.1073/pnas.1911497117.
29. Gill, D.; Parry, A.; Santos, F.; Okkenhaug, H.; Todd, C. D.; Hernando-Herraez, I.; Stubbs, T. M.; Milagre, I.; Reik, W. Multi-Omic Rejuvenation of Human Cells by Maturation Phase Transient Reprogramming. *Elife* **2022**, *11*. https://doi.org/10.7554/eLife.71624.
30. Hwang, S. G.; Kim, J. H.; Jo, S. Y.; Kim, Y. J.; Won, C. H. Cold Atmospheric Plasma Prevents Wrinkle Formation via an Antiaging Process. *Plasma Med* **2020**, *10* (2), 91–102. https://doi.org/10.1615/PlasmaMed.2020034810.
31. Downer, M.; Berry, C. E.; Parker, J. B.; Kameni, L.; Griffin, M. Current Biomaterials for Wound Healing. *Bioengineering* **2023**, *10* (12), 1378. https://doi.org/10.3390/bioengineering10121378.
32. Tören, E.; Mazari, A. A. Pullulan/Collagen Scaffolds Promote Chronic Wound Healing via Mesenchymal Stem Cells. *Micro* **2024**, *4* (4), 599–620. https://doi.org/10.3390/micro4040037.
33. Garau Paganella, L.; Bovone, G.; Cuni, F.; Labouesse, C.; Cui, Y.; Giampietro, C.; Tibbitt, M. W. Injectable Senolytic Hydrogel Depot for the Clearance of Senescent Cells. *Biomacromolecules* **2025**, *26* (2), 814–824. https://doi.org/10.1021/acs.biomac.4c00851.
34. Oh, S.; Kim, Y. H.; Kim, B. R.; Seo, H.-M.; Kwon, S.-H.; Choi, H.; Lee, H.; Na, J.-I.; Choi, C. P.; Ko, J. Y.; Ryu, H. J.; Seo, S. B.; Lee, J. H.; Kim, H. S.; Huh, C.-H. Real-World Clinical Practice on Skin Rejuvenation Among Korean Board-Certified Dermatologists: Survey-Based Results. *Ann Dermatol* **2025**, *37* (3), 123. https://doi.org/10.5021/ad.24.167.
35. Jang, D.; Shim, J.; Shin, D. M.; Noh, H.; Oh, S. J.; Park, J.; Lee, J. H. Magnesium Microneedle Patches for Under-eye Wrinkles. *Dermatol Ther* **2022**, *35* (9). https://doi.org/10.1111/dth.15732.
36. Lee, Y. J.; Kim, H. T.; Lee, W. J.; Chang, S. E.; Lee, M. W.; Choi, J. H.; Won, C. H. Anti-aging and Hydration Efficacy of a Cross-linked Hyaluronic Acid Microstructure Patch. *Dermatol Ther* **2019**, *32* (3). https://doi.org/10.1111/dth.12888.
37. Pandya, K.; Menendez, A.; MacAskill, M. G.; Gray, G. A.; Tavares, A. A. S. The Impact of Aging and Biological Sex on Cardiac Collagen Metabolism. *Mech Ageing Dev* **2025**, *226*, 112079. https://doi.org/10.1016/j.mad.2025.112079.
38. Tenkorang, M. A. A.; Chalise, U.; Daseke, I. M. J.; Konfrst, S. R.; Lindsey, M. L. Understanding the Mechanisms That Determine Extracellular Matrix Remodeling in the Infarcted Myocardium. *Biochem Soc Trans* **2019**, *47* (6), 1679–1687. https://doi.org/10.1042/BST20190113.
39. Hortells, L.; Johansen, A. K. Z.; Yutzey, K. E. Cardiac Fibroblasts and the Extracellular Matrix in Regenerative and Nonregenerative Hearts. *J Cardiovasc Dev Dis* **2019**, *6* (3), 29. https://doi.org/10.3390/jcdd6030029.
40. Jia, K.; Dai, Y.; Liu, A.; Li, X.; Wu, L.; Lu, L.; Bao, Y.; Jin, Q. Senolytic Agent Navitoclax Inhibits Angiotensin II-Induced Heart Failure in Mice. *J Cardiovasc Pharmacol* **2020**, *76* (4), 452–460. https://doi.org/10.1097/FJC.0000000000000878.
41. Lister, Z.; Rayner, K. J.; Suuronen, E. J. How Biomaterials Can Influence Various Cell Types in the Repair and Regeneration of the Heart after Myocardial Infarction. *Front Bioeng Biotechnol* **2016**, *4*. https://doi.org/10.3389/fbioe.2016.00062.
42. Choi, Y.; Jang, H.-S.; Shim, J.; Yeo, E.; Kim, M.-H.; Noh, H.; Oh, S.; Park, J.-H.; Lee, D.; Lee, J. H. 3D Keloid Spheroid Model: Development and Application for Personalized Drug Response Prediction. *Commun Biol* **2024**, *7* (1), 1470. https://doi.org/10.1038/s42003-024-07194-2.
43. Lei, Y.; Zhong, C.; Zhang, J.; Zheng, Q.; Xu, Y.; Li, Z.; Huang, C.; Ren, T. Senescent Lung Fibroblasts in Idiopathic Pulmonary Fibrosis Facilitate Non-Small Cell Lung Cancer Progression by Secreting Exosomal MMP1. *Oncogene* **2025**, *44* (11), 769–781. https://doi.org/10.1038/s41388-024-03236-5.
44. Hernandez-Gonzalez, F.; Prats, N.; Ramponi, V.; López-Domínguez, J. A.; Meyer, K.; Aguilera, M.; Muñoz Martín, M. I.; Martínez, D.; Agusti, A.; Faner, R.; Sellarés, J.; Pietrocola, F.; Serrano, M. Human Senescent Fibroblasts Trigger Progressive Lung Fibrosis in Mice. *Aging* **2023**, *15* (14), 6641–6657. https://doi.org/10.18632/aging.204825.
45. Sellarés, J.; Rojas, M. Quercetin in Idiopathic Pulmonary Fibrosis: Another Brick in the Senolytic Wall. *Am J Respir Cell Mol Biol* **2019**, *60* (1), 3–4. https://doi.org/10.1165/rcmb.2018-0267ED.
46. Nambiar, A.; Kellogg, D.; Justice, J.; Goros, M.; Gelfond, J.; Pascual, R.; Hashmi, S.; Masternak, M.; Prata, L.; LeBrasseur, N.; Limper, A.; Kritchevsky, S.; Musi, N.; Tchkonia, T.; Kirkland, J. Senolytics Dasatinib and Quercetin in Idiopathic Pulmonary Fibrosis: Results of a Phase I, Single-Blind, Single-Center, Randomized, Placebo-Controlled Pilot Trial on Feasibility and Tolerability. *EBioMedicine* **2023**, *90*, 104481. https://doi.org/10.1016/j.ebiom.2023.104481.
47. Krizhanovsky, V.; Yon, M.; Dickins, R. A.; Hearn, S.; Simon, J.; Miething, C.; Yee, H.; Zender, L.; Lowe, S. W. Senescence of Activated Stellate Cells Limits Liver Fibrosis. *Cell* **2008**, *134* (4), 657–667. https://doi.org/10.1016/j.cell.2008.06.049.
48. Cheng, N.; Kim, K.-H.; Lau, L. F. Senescent Hepatic Stellate Cells Promote Liver Regeneration through IL-6 and Ligands of

DOI: 10.36838/IJHSR86.55

CXCR2. *JCI Insight* **2022**, *7* (14). https://doi.org/10.1172/jci.insight.158207.
49. Xing, Y.; Zhu, J. Role of Cellular Senescence in Hepatic Diseases (Review). *Int J Mol Med* **2025**, *56* (5), 1–26. https://doi.org/10.3892/ijmm.2025.5623.
50. Du, K.; Umbaugh, D. S.; Wang, L.; Jun, J. H.; Dutta, R. K.; Oh, S. H.; Ren, N.; Zhang, Q.; Ko, D. C.; Ferreira, A.; Hill, J.; Gao, G.; Pullen, S. S.; Jain, V.; Gregory, S.; Abdelmalek, M. F.; Diehl, A. M. Targeting Senescent Hepatocytes for Treatment of Metabolic Dysfunction- Associated Steatotic Liver Disease and Multi-Organ Dysfunction. *Nat Commun* **2025**, *16* (1), 3038. https://doi.org/10.1038/s41467-025-57616-w.
51. Dai, Q.; Jiang, W.; Huang, F.; Song, F.; Zhang, J.; Zhao, H. Recent Advances in Liver Engineering With Decellularized Scaffold. *Front Bioeng Biotechnol* **2022**, *10*. https://doi.org/10.3389/fbioe.2022.831477.
52. Li, C.; Shen, Y.; Huang, L.; Liu, C.; Wang, J. Senolytic Therapy Ameliorates Renal Fibrosis Postacute Kidney Injury by Alleviating Renal Senescence. *The FASEB Journal* **2021**, *35* (1). https://doi.org/10.1096/fj.202001855RR.
53. Mylonas, K. J.; Ferenbach, D. A. Targeting Senescent Cells as Therapy for CKD. *Kidney360* **2024**, *5* (1), 142–151. https://doi.org/10.34067/KID.0000000000000316.
54. Xu, J.; Zhou, L.; Liu, Y. Cellular Senescence in Kidney Fibrosis: Pathologic Significance and Therapeutic Strategies. *Front Pharmacol* **2020**, *11*. https://doi.org/10.3389/fphar.2020.601325.
55. Ansari, Md. M.; Ghosh, M.; Lee, D.-S.; Son, Y.-O. Senolytic Therapeutics: An Emerging Treatment Modality for Osteoarthritis. *Ageing Res Rev* **2024**, *96*, 102275. https://doi.org/10.1016/j.arr.2024.102275.
56. Gil, T.-H.; Zheng, H.; Lee, H. G.; Shin, J.-W.; Hwang, S. W.; Jang, K.-M.; Jeon, O. H. Senolytic Drugs Relieve Pain by Reducing Peripheral Nociceptive Signaling without Modifying Joint Tissue Damage in Spontaneous Osteoarthritis. *Aging* **2022**, *14* (15), 6006–6027. https://doi.org/10.18632/aging.204204.
57. Li, S.; Wang, N.; Dong, Q.; Dong, M.; Qu, M.; Wang, Y.; Shi, W. The Senescence Difference between the Central and Peripheral Cornea Induced by Sutures. *BMC Ophthalmol* **2023**, *23* (1), 169. https://doi.org/10.1186/s12886-023-02917-1.
58. Wang, X.; Qu, M.; Li, J.; Danielson, P.; Yang, L.; Zhou, Q. Induction of Fibroblast Senescence During Mouse Corneal Wound Healing. *Investigative Opthalmology & Visual Science* **2019**, *60* (10), 3669. https://doi.org/10.1167/iovs.19-26983.
59. Shi, L.; Zhao, Y.; Fei, C.; Guo, J.; Jia, Y.; Wu, D.; Wu, L.; Chang, C. Cellular Senescence Induced by S100A9 in Mesenchymal Stromal Cells through NLRP3 Inflammasome Activation. *Aging* **2019**, *11* (21), 9626–9642. https://doi.org/10.18632/aging.102409.
60. Hernandez-Segura, A.; de Jong, T. V.; Melov, S.; Guryev, V.; Campisi, J.; Demaria, M. Unmasking Transcriptional Heterogeneity in Senescent Cells. *Current Biology* **2017**, *27* (17), 2652-2660.e4. https://doi.org/10.1016/j.cub.2017.07.033.
61. Hiebert, P.; Wietecha, M. S.; Cangkrama, M.; Haertel, E.; Mavrogonatou, E.; Stumpe, M.; Steenbock, H.; Grossi, S.; Beer, H.-D.; Angel, P.; Brinckmann, J.; Kletsas, D.; Dengjel, J.; Werner, S. Nrf2-Mediated Fibroblast Reprogramming Drives Cellular Senescence by Targeting the Matrisome. *Dev Cell* **2018**, *46* (2), 145-161.e10. https://doi.org/10.1016/j.devcel.2018.06.012.
62. He, Y.; Zhang, X.; Chang, J.; Kim, H.-N.; Zhang, P.; Wang, Y.; Khan, S.; Liu, X.; Zhang, X.; Lv, D.; Song, L.; Li, W.; Thummuri, D.; Yuan, Y.; Wiegand, J. S.; Ortiz, Y. T.; Budamagunta, V.; Elisseeff, J. H.; Campisi, J.; Almeida, M.; Zheng, G.; Zhou, D. Using Proteolysis-Targeting Chimera Technology to Reduce Navitoclax Platelet Toxicity and Improve Its Senolytic Activity. *Nat Commun* **2020**, *11* (1), 1996. https://doi.org/10.1038/s41467-020-15838-0.
63. González-Gualda, E.; Pàez-Ribes, M.; Lozano-Torres, B.; Macias, D.; Wilson, J. R.; González- López, C.; Ou, H.; Mirón-Barroso, S.; Zhang, Z.; Lérida-Viso, A.; Blandez, J. F.; Bernardos, A.; Sancenón, F.; Rovira, M.; Fruk, L.; Martins, C. P.; Serrano, M.; Doherty, G. J.; Martínez-Máñez, R.; Muñoz-Espín, D. Galacto-conjugation of Navitoclax as an Efficient Strategy to Increase Senolytic Specificity and Reduce Platelet Toxicity. *Aging Cell* **2020**, *19* (4). https://doi.org/10.1111/acel.13142.
64. Ovadya, Y.; Landsberger, T.; Leins, H.; Vadai, E.; Gal, H.; Biran, A.; Yosef, R.; Sagiv, A.; Agrawal, A.; Shapira, A.; Windheim, J.; Tsoory, M.; Schirmbeck, R.; Amit, I.; Geiger, H.; Krizhanovsky, V. Impaired Immune Surveillance Accelerates Accumulation of Senescent Cells and Aging. *Nat Commun* **2018**, *9* (1), 5435. https://doi.org/10.1038/s41467-018-07825-3.
65. Waters, D. W.; Blokland, K. E. C.; Pathinayake, P. S.; Burgess, J. K.; Mutsaers, S. E.; Prele, C. M.; Schuliga, M.; Grainge, C. L.; Knight, D. A. Fibroblast Senescence in the Pathology of Idiopathic Pulmonary Fibrosis. *American Journal of Physiology-Lung Cellular and Molecular Physiology* **2018**, *315* (2), L162–L172. https://doi.org/10.1152/ajplung.00037.2018.
66. Dutta, B.; Goswami, R.; Rahaman, S. O. TRPV4 Plays a Role in Matrix Stiffness-Induced Macrophage Polarization. *Front Immunol* **2020**, *11*. https://doi.org/10.3389/fimmu.2020.570195.
67. Ke, Y.; Wang, X. J. TGFβ Signaling in Photoaging and UV-Induced Skin Cancer. *J Invest Dermatol* **2021**, *141* (5), 1104–1110. https://doi.org/10.1016/j.jid.2020.11.007.
68. Amor, C.; Feucht, J.; Leibold, J.; Ho, Y.-J.; Zhu, C.; Alonso-Curbelo, D.; Mansilla-Soto, J.; Boyer, J. A.; Li, X.; Giavridis, T.; Kulick, A.; Houlihan, S.; Peerschke, E.; Friedman, S. L.; Ponomarev, V.; Piersigilli, A.; Sadelain, M.; Lowe, S. W. Senolytic CAR T Cells Reverse Senescence-Associated Pathologies. *Nature* **2020**, *583* (7814), 127–132. https://doi.org/10.1038/s41586-020-2403-9.
69. Kaur, P.; Otgonbaatar, A.; Ramamoorthy, A.; Chua, E. H. Z.; Harmston, N.; Gruber, J.; Tolwinski, N. S. Combining Stem Cell Rejuvenation and Senescence Targeting to Synergistically Extend Lifespan. *Aging* **2022**. https://doi.org/10.18632/aging.204347.

Author

Youn-Jean Han is a student at Ewha Girls' High School in Seoul, Republic of Korea. Based on multiple internship experiences related to biomedical sciences, she has developed a strong academic interest in senotherapeutics and anti-aging research. She hopes to continue studying biomedical and aging sciences in the future.