INFLAMM-AGING: A MECHANISM OF AGING THAT CONTRIBUTES TO THE CHARACTERISTICS OF SKIN INVOLVEMENT IN SYSTEMIC SCLEROSIS

Neslihan Gokcen¹
https://orcid.org/0000-0003-3022-493X

¹Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey
E-mail: drngokcen@hotmail.com
Twitter handle: @NeslihanGken7

Submission date: May 22, 2022
Acceptance date: May 31, 2022

How to cite: Gokcen N. Inflamm-aging: a mechanism of aging that contributes to the characteristics of skin involvement in systemic sclerosis. Anti Aging East Eur 2022;1(1): 47-51. https://doi.org/10.56543/aaeeu.2022.1.1.07

Abstract
Aging is associated with deterioration of the immune function. Two contributory mechanisms are inflamm-aging, which is a chronic, low-grade systemic inflammation, and immunosenescence, an impairment of adaptive immune function that may also contribute to the development of inflamm-aging. This age-related inflammatory event is associated with alteration to the balance of pro-inflammatory and anti-inflammatory cytokines. The effect of inflamm-aging on skin aging in healthy people is accepted; however, its effect on normal skin aging and/or skin characteristics in systemic sclerosis is unknown. The hypothesis presented herein suggests that inflamm-aging may contribute to the evolution of the skin phases in systemic sclerosis, which progress from edematous, fibrotic, and indurative phases to the atrophic phase.

Keywords: Atrophy, cell senescence, skin aging, systemic sclerosis

Introduction
Aging is an inevitable process that results in permanent weakening in functionality and reproducibility over time [1]. As the largest organ of the body, skin is essential to maintain the balance between the external environment and internal tissues. As a result of complex aging mechanisms, including genetic/epigenetic factors, environmental factors, and inflammation, the skin undergoes changes in appearance and function [2-4]. Among the many factors that contribute to aging, chronic subclinical systemic inflammation, also termed inflamm-aging, and impairment of the adaptive immune system, called immunosenescence, are thought to be important, recently identified contributors [5]. Inflamm-aging, emerging as a consequence of immunosenescence, is an age-related inflammatory condition, which is associated with changes in the balance of pro-inflammatory and anti-inflammatory mediators. This change occurs in order to maintain immune homeostasis and compensate for the changes but constant exposure to chronic inflammation will accelerate aging [6].

Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by fibrotic changes in the skin and internal organs, which cause high disability, morbidity, and mortality [7]. Patients with SSc present with various manifestations, such as cutaneous fibrosis, digital ulcers, and musculoskeletal, pulmonary, renal, and gastrointestinal involvement [8,9]. Skin involvement is the most prominent feature of this disease and is used to categorize patients into two subgroups according to the degree of skin involvement.
involvement; these are limited (lcSSc) and diffuse systemic sclerosis (dcSSc) [9]. Furthermore, skin involvement shows different characteristics according to the disease duration. Three phases have been identified: i) an edematous phase lasting 6-12 months; ii) a fibrotic or indurative phase lasting 1-4 years or longer; and iii) an atrophic phase that lasts for rest of the life of the patient [10].

A recent study investigated whether normal aging might help to improve skin involvement of patients with SSc over time [11]. The authors found that skin stiffness determined by shear wave elastography was significantly reduced with aging in both SSc patients and healthy controls, suggesting that inflamm-aging might be the cause of this improvement. Here, the current hypothesis suggests that inflamm-aging, a well-defined component of aging, may contribute to the evolution of skin phases in SSc from edematous, fibrotic and indurative phases towards the atrophic phase.

**The mechanism of skin aging**

In general, aging is investigated under two main subtypes: intrinsic and extrinsic aging. Intrinsic aging ensues from slow tissue deterioration, changes in hormonal status, and metabolic reactions, while extrinsic aging is mainly associated with external elements, such as ultraviolet radiation and tobacco use [12]. Even though these subtypes of aging seem to have different mechanisms that trigger skin aging, they are actually intertwined. For instance, chronic ultraviolet exposure promotes oxidative stress, which is well known metabolic reaction causing senescence [2,13].

The effects of both internal and external aging on the epidermis and dermis are described in detail in the literature. The epidermis is a stratified epithelium containing tightly bound cells, commonly known as keratinocytes, which proliferate in the basal layer and thus maintain tissue balance. The source of these keratinocytes is stem cells located in the bulge region of hair follicles and in the interfollicular epidermis. Keratinocytes also provide a link to dermal tissue in association with the basement membrane. With aging, the epidermis becomes thinner and the healing of the epidermal barrier is impaired [14,15]. Even though keratinocytes are the main cell type in the epidermis, melanocytes, the cell producing pigment to protect people from ultraviolet radiation, are also located in the epidermis. Melanocytes play a crucial role in networking with Langerhans cells, a specialized subset of dendritic cells that are the part of immune system. The factors related to aging mostly damage intercellular connection, promoting epidermal immune dysfunction and pigment dysregulation [14].

The dermis is composed of an extracellular matrix of collagenous, elastic fibers, and glycosaminoglycans, which are fibrillar proteins produced by the predominant cells, fibroblasts [13,15,16]. Besides fibroblasts, the dermis comprises dendritic cells, macrophages, mast cells, and other cells of the immune system. Moreover, this layer contains nerve endings, Schwann cells, blood and lymph vessels, hair follicles and sweat glands. With aging, the structure of the dermis deteriorates due to disorganized extracellular matrix (ECM) formation after changes in ECM protein turnover or accumulation of post-translational modifications [1,14]. These alterations in the dermis cause wrinkles and sagging of skin [16].

Cell aging is an important component that paves the way for skin aging. Adaptive immunity declines with increasing age and so immune function worsens, a process termed immunosenescence. Reduction in response of immune system to new challenges leads to deterioration in proportions of T cells, along with a more restricted receptor repertoire and consequent decrease in antibody diversity. Low-grade continuum systemic inflammation, known as inflamm-aging and caused by immunosenescence, is associated with an elevation in the serum levels of inflammatory cytokines, such as IL-6, IL-8, and TNF-alpha, which, as expected, provoke the emergence of age-related inflammatory diseases, such as type 2 diabetes and Alzheimer’s disease. Even though the effect of inflamm-aging on aging is well-known, its role in skin aging is still little known [2,12,16].

Senescence is vital to maintain the physiological balance in normal tissue, preventing fibrosis while tissue heals. However, with aging, the balance between senescence and immune homeostasis deteriorates. Accordingly, the key cells, including epidermal keratinocytes and melanocytes, and dermal fibroblasts, become metabolically active, even though they are unable to divide. In addition, decreased Langerhans cells, leading to impaired tolerance to self-antigens, and dysfunctional CD4+ T cells causing the release of proinflammatory cytokines, trigger
Inflamm-aging in the skin. Over time, these senescent cells accumulate in the skin and are associated with the production of enzymes, including matrix metalloproteinases, serine proteases, and cathepsins, leading to alteration of the morphology of the elastic fibers, and consequently weakening of skin strength and elasticity. All in all, immunosenescence and inflamm-aging cause skin aging by changing the morphology of the ECM [2,16].

Skin involvement and inflamm-aging in SSc

Three key factors involved in the pathogenesis of SSc are genetic/epigenetic mechanisms, vascular injury, and immune dysregulation, which all result in progressive fibrosis [17-19]. The pathogenesis of SSc is rather complicated. Therefore, herein, the role of the immune system in the pathogenesis of SSc will be examined, while largely disregarding the genetic/epigenetic and vascular factors.

Dysfunction of endothelial cells is the key event in the pathogenesis of SSc vasculopathy, which causes immune system activation. In addition to the recruitment of inflammatory cells caused by activated endothelial cells, changes in both innate and adaptive immune responses are observed in the early stage of SSc, which result in altered function of inflammatory cells. From the perspective of cells, T cells (CD4+ T cells) (especially type 2 T helper (Th2) cells are more common in SSc than Th1), T regulatory (Treg) cells, T follicular helper (TFh)-like cells, Th17 and Th22 cells, plasmacytoid dendritic cells, myofibroblasts, mesenchymal stromal cells, monocyte-derived dendritic cells, monocytes, and macrophages play an important role in the pathogenesis of SSc [17,20,21]. After the change in immune responses, a prominent type I interferon (IFN) signature emerges and elevated IFN levels are detected in the blood and skin. Th2 cells secrete IL-4 and IL-13, known as pro-fibrotic cytokines, while Th1 cells, down-regulated in SSC, secrete anti-fibrotic IFNγ. Transforming growth factor-beta (TGF-β), a pro-fibrotic cytokine, is secreted by inflammatory cells such as macrophages. Dermal fibroblasts produce periostin, which is closely associated with cutaneous involvement [20,22]. Myofibroblasts, which are activated fibroblasts, are responsible for producing collagen and ECM proteins. The activation of fibroblasts is induced by TGF-β signal pathway and focal adhesion signaling pathways [7].

Skin biopsies in SSc demonstrate the presence of abundant cytotoxic CD4+ T cells with enhanced metabolic activity, leading to apoptotic death of various cellular subtypes, and increased numbers of myofibroblasts induced by activated mesenchymal stromal cells (MSCs), all of which result in excessive tissue repair and fibrosis [20]. Although many studies have investigated the pathogenesis of skin involvement in SSc, research into immunosenescence and inflamm-aging in these patients is scarce. As in normal aging, in SSc low-grade inflammation and oxygen radicals trigger DNA damage, inducing a DNA damage response and a stress-induced response. The DNA damage response is associated with the appearance of the senescence-associated secretory phenotype (SASP), which is defined by the profile of proteins secreted by senescence cells. These responses cause an increase in growth factor, proinflammatory cytokines, and extracellular proteases, all of which influence immune adaptation, leading to the up-regulation of effector and memory T cells, natural killer cells and myeloid cells, and the reduction of the T cell repertoire. Accordingly, this process results in immunosenescence and inflamm-aging, with increased levels of cytokines, such as IL-1β, IL-6, and TNF-alpha, which provoke fibrosis in SSc [6].

Inflammasome affects the characteristics of skin involvement in SSc

Immunosenescence and inflamm-aging are inevitable processes, influencing all individuals regardless of their health status [5]. In line with the mounting evidence, some signaling pathways, such as NF-κB, sirtuins, Wnt, and TGF-β pathways are closely linked with inflammation, cellular senescence, cancer, and age-related disease [6]. Notably, after an increase in profibrotic cytokines such as IL-1β, IL-6, and TNF-alpha, which cross talk with TGF-β signaling at multiple levels, myofibroblasts are activated. These apoptosis-resistant myofibroblasts produce not only ECM proteins but also many profibrotic mediators, including TGF-β, causing abundant fibrosis [17,20]. It seems reasonable that these processes, immunosenescence and inflammasome, probably induce fibrosis in SSc. However, senescent cells result in loss of proteostasis (quantitative and qualitative homeostasis of the cellular proteome) and impaired dermal ECM, causing skin aging.
In the expected clinical course, skin characteristics in SSc move through phases over time from the edematous phase to the fibrotic/indurative, and finally the atrophic phase [10]. It is estimated that all these phases have different skin thickness; the first two phases are related to increased skin thickness while the atrophic phase is characterized by decreased thickness. Consistent with this prediction, it has been shown that cutaneous thickness decreases from the edematous phase to the atrophic phase as the clinical phase progresses [23]. In a recent study, patients with SSc and healthy controls were followed for 5 years in order to assess the course of their skin stiffness using shear wave elastography [11]. These authors demonstrated that skin stiffness decreased significantly in both SSc patients and healthy controls over time, concluding that this could be explained by normal skin aging. Therefore, inflamm-aging seems to favor the transition of the skin to the atrophic phase in SSc.

**Conclusion**

Here, this hypothesis presents that inflamm-aging may play a role in the evolution of skin phases in SSc, from edematous, fibrotic and indurative phases to the atrophic phase. Even though there are several studies investigating its effect on skin aging in healthy people, there is insufficient data on its influence on skin aging and cutaneous evolution in SSc. Thus, evaluating the impact of inflamm-aging on the skin in SSc is important to fully understand the mechanism of the evolution of skin involvement in these patients, taking into account the normal skin aging process as a result of inflamm-aging.

**FUNDING**

None

**AUTHOR CONTRIBUTIONS**

The author has contributed to the conception or design of the study, analysis, and interpretation of the data. The author edited the manuscript and accepted its final form.

**CONFLICTS OF INTEREST**

The author declares no conflicts of interest with respect to the authorship and/or publication of this article.

**DISCLAIMER**

No part of this manuscript is copied from or published elsewhere.

**ACKNOWLEDGEMENTS**

I would like to thank Mr. Jeremy Jones, of the Kocaeli University Academic Writing Department, for the revisions of the English in this paper.

**REFERENCES**

1. Csekés E, Račková L. Skin Aging, Cellular Senescence and Natural Polyphenols. Int J Mol Sci 2021;22(23):12641.
2. Pilkington SM, Bulfone-Pauser S, Griffiths CEM, Watson REB. Inflammaging and the Skin J Invest Dermatol. 2021;141(45):1087-1095.
3. Sanada F, Taniyama Y, Muratsu J, Otsu R, Shimizu H, Rakugi H, Morishita R. Source of Chronic Inflammation in Aging. Front Cardiovasc Med 2018;5:12.
4. Chen Y, Lyga J. Brain-skin connection: stress, inflammation and skin aging. Inflamm Allergy Drug Targets 2014;13(3):177-90.
5. Bonafe M, Pratichizzo F, Giuliani A, Storci G, Sabbatinielli J, Olivieri F. Inflamm-aging: Why older men are the most susceptible to SARS-CoV-2 complicated outcomes. Cytokine Growth Factor Rev 2020;53:33-37.
6. Shen CY, Lu CH, Wu CH, Li KJ, Kuo YM, Hsieh SC, Yu CL. Molecular Basis of Accelerated Aging with Immune Dysfunction-Mediated Inflammation (Inflamm-Aging) in Patients with Systemic Sclerosis. Cells 2021;10(12):3402.
7. Mei X, Zhao H, Huang Y, Tang Y, Shi X, Pu W, et al. Involvement of Disabled-2 on skin fibrosis in systemic sclerosis. J Dermatol Sci 2020;99(1):44-52.
8. Starnoni M, Pappalardo M, Spinella A, Testoni S, Lattanzi M, Femia R, et al. Systemic sclerosis cutaneous expression: Management of skin fibrosis and digital ulcers. Ann Med Surg (Lond) 2021;71:102984.
9. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390(10103):1685-1699.
10. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Rheumatol 2017;2(1):11-18.
11. Santiago T, Santiago M, Coutinho M, Salvador MJ, Da Silva JAP. How much of skin improvement over time in systemic sclerosis is due to normal ageing? A prospective study with shear-wave elastography. Arthritis Res Ther 2020;22(1):50.
12. de Araújo R, Lóbo M, Trindade K, Silva DF, Pereira N. Fibroblast Growth Factors: A Controlling Mechanism of Skin Aging. Skin Pharmacol Physiol 2019;32(5):275-282.
13. Egbert M, Ruetze M, Sattler M, Wenck H, Gallinat S, Lucius R, Weise JM. The matricellular protein periostin contributes to proper collagen function and is downregulated during skin aging. J Dermatol Sci 2014;73(1):40-8.

14. Gruber F, Kremslehner C, Eckhart L, Tschachler E. Cell aging and cellular senescence in skin aging - Recent advances in fibroblast and keratinocyte biology. Exp Gerontol 2020;130:110780.

15. Püllen R, Konrad J, Merkel R, Hoffmann B. Skin under Strain: From Epithelial Model Tissues to Adult Epithelia. Cells 2020;130:110780.

16. Letsiou S. Tracing skin aging process: a mini-review of in vitro approaches. Biogerontology 2021;22(3):261-272.

17. Cutolo M, Soldano S, Smith V. Pathophysiology of systemic sclerosis: current understanding and new insights. Expert Rev Clin Immunol 2019;15(7):753-764.

18. Stifano G, De Palma R. Editorial: Etiopathogenesis of Systemic Sclerosis: An Update. Front Immunol 2021;12:663381.

19. Brown M, O'Reilly S. The immunopathogenesis of fibrosis in systemic sclerosis. Clin Exp Immunol 2019;195(3):310-321.

20. Di Battista M, Barsotti S, Orlandi M, Lepri G, Codullo V, Della Rossa A, et al. One year in review 2021: systemic sclerosis. Clin Exp Rheumatol 2021;39 Suppl 131(4):3-12.

21. Gaydosik AM, Tabib T, Domsic R, Khanna D, Lafyatis R, Fuschiotti P. Single-cell transcriptome analysis identifies skin-specific T-cell responses in systemic sclerosis. Ann Rheum Dis 2021;80(11):1453-1460.

22. Arron JR. Biomarkers in systemic sclerosis: mechanistic insights into pathogenesis and treatment. Curr Opin Rheumatol 2021;33(6):480-485.

23. Kaloudi O, Bandinelli F, Filippucci E, Conforti ML, Miniati I, Guiducci S, et al. High frequency ultrasound measurement of digital dermal thickness in systemic sclerosis. Ann Rheum Dis 2010;69(6):1140-3.