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Inflammaging in Dermatology: A New Frontier for Research

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ABSTRACT

As humans age, our ability to manage certain types of inflammation is reduced. As a result, we experience chronic, low-grade inflammation, which has been termed "inflammaging". This type of low-level inflammation is driven by a progressive increase in pro-inflammatory systemic cytokines over time. Inflammaging is thought to contribute to many age-related chronic diseases including cardiovascular disease, diabetes, Alzheimer's disease, and even certain cancers. Recent studies suggest that the human microbiome may play a critical role in inflammaging. As the largest organ of the body and home to a significant portion of the human microbiome, the skin may play a unique role in inflammaging. In this review article, we present common dermatological diseases through the lens of inflammaging, look at how our skin may play a role in reducing inflammaging, and highlight the need for further focused research in this area.

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INTRODUCTION

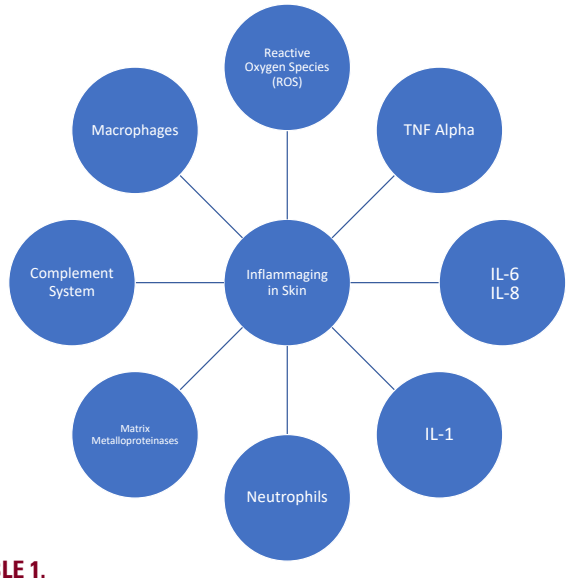
As humans continue to live longer, there is an increased interest in research on age-related physiologic changes and illnesses. This study of aging and its link to age-related chronic conditions has given rise to a new research field called geroscience. Geroscientists assume that the mechanisms that drive aging and those that drive age-related diseases largely overlap. Thinking along these lines, in 2000, Claudio Franceschi developed the concept of "inflammaging", driving researchers to recognize that aging is a complex and multifaceted phenomenon that demands a holistic view of the body's physiology.[1-3] Franceschi initially described inflammaging as an extension on the network theory of aging; he proposed that a reduction in the ability to cope with stressors, coupled with a progressive increase in proinflammatory status was the cause of inflammaging.[4] He proposed that aging is associated with a chronic, sterile, low-grade inflammation called inflammaging.[5]

It is important to distinguish between inflammaging and acute, transient inflammation. Transient inflammation in the face of tissue injury or invading pathogens is beneficial as a defensive immune response, but when individuals have persistently elevated levels of inflammation, that process is considered inflammaging, and thus detrimental. Inflammaging is thought to contribute to many age-related chronic diseases including cardiovascular disease, diabetes, Alzheimer's disease, and certain cancers. A number of other studies have looked at the role of proinflammatory cytokines and found that IL-6 and CRP – two common markers of inflammaging – were strong predictors of physical and cognitive performance. In addition, these markers were strong predictors of mortality in the elderly population.[6-10]

Recent advancements in geroscience have come to conclude that inflammaging does not exist in isolation; instead, a plethora of studies have linked inflammaging with immunosenescence as a contributing factor. Immunosenescence is a collection of age-related changes in the adaptive immune system. Immunosenescence refers to the concept that the adaptive immune system (ie, B cells and T cells) becomes less effective with age and the innate immune system (ie, neutrophils, macrophages, natural killer cells) becomes more dominant.[11-14] Other key factors thought to contribute to inflammaging include microbiome dysbiosis and oxidative stress.[15-17] This is of particular importance to dermatologists given that the skin is home to a large portion of the human microbiome and plays a key role in the prevention of oxidative stress due to biological or environmental agents.[18] As such, it follows that our body's largest organ, the skin, may be responsible for a larger role in promoting or preventing inflammaging.

In this review article, we present common dermatological diseases through the lens of inflammaging, look at how our skin may play a central role in reducing inflammaging, and highlight the need for further focused research in this area. Management of the human microbiome in the skin may even have an impact on chronic disease.

FIGURE 1. Mediators of Inflammaging in the Skin.



Inflammaging in Dermatology

We reviewed the existing, published literature to understand the current state of research in dermatology regarding inflammaging and the skin. We searched the following key words: "inflammaging" + "skin", "inflammaging" + "dermatology", "inflammageing" + "skin", "inflammageing" + "dermatology". After eliminating articles that were not relevant to dermatology, we found 15 articles focusing on inflammaging in dermatology. These covered a variety of topics from UV-induced inflammaging to the anti-inflammaging properties of certain botanicals. The articles and abstracts are summarized in Table 1.

As a number of the articles from our search indicate, inflammaging in the skin is known to be a multifaceted and sophisticated pathological process influenced by reactive oxygen species (ROS), TNF-alpha, IL-1, IL-6, IL-8, neutrophils, matrix metalloproteinases (MMPs), the complement system, and

TABLE 1.

Existing Research Publications Relating to Inflammaging and Dermatology Organized by Category

Author et al	Year	Title	Main Topic	Sample	Results
Newman, J	2018	Profiling inflammageing and senescence factors in skin tissue as a strategy to uncover novel biomarkers of ageing.	Inflammaging factors in skin tissue	Abstract	A significant increase in two markers – p21, a marker of senescence, and IL-6, a marker of inflammation and a marker of the senescence associated secretory phenotype (SASP) was demonstrated in vivo across multiple patient samples. They noted that p21-positive cells have an increased level of perinuclear interleukin-6 and could indicate how senescent cells interact and modify their environment by creating chronic local inflammation. The paper also described how senescent cells may contribute to inflammaging in tissues, potentially providing evidence that limiting the inflammatory effects of senescent cells could be a prospective therapeutic target for the future.
Yap WN	2017	Tocotrienol-rich fraction attenuates UV-induced inflammaging: A bench to bedside study.	UV-induced inflammaging of the skin	20 human subjects	This study concluded that tocotrienol rich fraction (TRF) may serve as an anti-inflammatory compound that is safe to be applied daily to protect the skin from UV-induced inflammaging.
Scheurmann J	2013	Mice with heterozygous deficiency of manganese superoxide dismutase (SOD2) have a skin immune system with features of "inflamm-aging."	Mice SOD2-deficiency resulting in inflammaging – specifically via the cutaneous immune system	Mice and human tissue donors	Authors concluded that super oxide dismutase 2 (SOD2) is a molecular candidate in the regulation of inflammaging as it may convey both immunosuppressive and proinflammatory signals through alteration of skin dendritic cells and T-cell functions.
Suggs A	2014	Effect of botanicals on inflammation and skin aging: analyzing the evidence.	Effect of botanicals on inflammation and skin aging	Commercially available products with novel botanicals	This review concluded that argan oil, rosemary, pomegranate, coenzyme Q10, and coffeeberry lack clinical data to support the anti-aging claims made by commercially available products containing them.
Zhuang Y	2014	Inflammaging in skin and other tissues - the roles of complement system and macrophage.	Inflammaging's role in the skin through the complement system	Review article	The authors concluded that understanding the mechanisms of how complement and macrophages result in skin aging and age-related skin diseases will help provide new paths for dermatologists and researchers to develop therapeutics.

TABLE 1. (CONTINUED)

Existing Research Publications Relating to Inflammaging and Dermatology Organized by Category					
Author et al	**Year**	**Title**	**Main Topic**	**Sample**	**Results**
Qin Z	2013	Elevated cysteine-rich protein 61 (CCN1) promotes skin aging via upregulation of IL-1β in chronically sun-exposed human skin.	UV-induced aging of the skin	6 human skin punch biopsies	Cysteine-rich protein 61 (CCN1) is upregulated in the dermis in vivo by acute UV exposure and elevated in chronically sun-exposed prematurely aged human skin. Elevated CCN1 upregulates IL-1β, which in turn inhibits collagen production and promotes collagen degradation.
Prattichizzo F	2016	Anti-TNF-α treatment modulates SASP and SASP-related microRNAs in endothelial cells and in circulating angiogenic cells.	Reduction of inflammaging via adalimumab's effects on TNF-alpha	10 psoriatic patients and purchased donor pools and cells	Adalimumab can cause epigenetic changes in cells undergoing senescence, thus contributing to the attenuation of SASP tumor- promoting effects. Restraining the SASP could help delay age-related disease onset and progression, particularly in patients with an established chronic inflammatory background.
Doles J	2012	Age-associated inflammation inhibits epidermal stem cell function.	Age related inflammation on epidermal stem-cell function	Mice	There may be an age-associated imbalance in epidermal Jak–Stat signaling that inhibits stem cell function. This study reveals a role for the aging epidermis in the disruption of cytokine and stem cell homeostasis, suggesting that stem cell decline during aging may be part of broader tumor-suppressive mechanisms.
Goto M	2016	Inflammageing assessed by MMP9 in normal Japanese individuals and the patients with Werner syndrome.	Inflammaging and Werner syndrome	217 aged humans and 41 Werner syndrome patients	Their previous study reported an increase in the serum CRP among normal ageing and patients with Werner syndrome (WS). This study showed that serum matrix metalloproteinase-9 (MMP9) levels were elevated in normal ageing but decreased in WS.
Antonicelli F	2014	Matrix metalloproteinases and skin inflammaging.	Role of MMPs in UV-induced aging of the skin	Review article	The authors concluded that disorganization of dermal collagen and elastin fibers may release elastokines. Elastokines are peptides containing a DNA specific motif. They are similar to cytokines and may play a role in skin inflammaging.
Maramaldi G	2013	Anti-inflammaging and antiglycation activity of a novel botanical ingredient from African biodiversity (Centevita™).	Use of C. Asiatica as an anti-inflammatory	Human explants from 1 person and clinical study on 20 volunteers	The topical efficacy of a purified extract from Madagascar, Centella asiatica, was tested on human explants and human volunteers. The extract protected DNA from UV -induced damage, decreasing the thymine photodimerization by over 28% ($P<0.05$) and reduced (26%, $P<0.01$) expression of interleukin-1α.
Kim M	2019	Particulate matter induces pro-inflammatory cytokines via phosphorylation of p38 MAPK possibly leading to dermal inflammaging.	Effect of particulate matter (PM) on skin ageing	Co-culture of human keratinocytes (HaCaT) and fibroblasts (HDF)	PMs induce the expression of pro-inflammatory cytokines in keratinocytes via the p38 MAPK pathway. The results suggest that PMs may trigger skin ageing via p38 MAPK activation and interleukin secretion in epidermal keratinocytes.
Chajra H	2019	An efficient means to mitigate skin inflammaging by inhibition of the NLRP3 inflammasome and Nfkb pathways: A Novel Epigenetic Mechanism	Use of brown seaweed (*Laminaria Japonica*) extract as an efficient skin anti-inflammaging active ingredient	6 humans	The authors discuss that the innate immune system involves two different inflammatory pathways: inflammasomes (ex. NLRP3) and Nfkb. The pathways are induced by double stranded RNA dependent protein kinase (PKR). The authors report that *Laminaria Japonica* appears to inhibit these two pathways. This in turn reduces reactive oxygen species and proinflammatory cytokines. They propose that this extract may offer a novel approach to reduce skin inflammaging.
Velarde MC	2017	Epidermal barrier protects against age-associated systemic inflammation.	Epidermal barrier malfunction and systemic inflammation	Humans and mice	Disruption of the epidermal barrier increases serum cytokine levels perhaps partly because of increased cytokine production by the skin. Authors concluded that restoring the epidermal barrier in aged mice may reduce circulating levels of proinflammatory cytokines.
Golomb L	2015	Age-associated inflammation connects RAS-induced senescence to stem cell dysfunction and epidermal malignancy.	Ageing induced inflammation and neoplasm	Mice	The authors concluded that there may be an age-dependent link between the accumulation of senescent cells in the skin, immune infiltration and cancer progression. This in turn, could contribute to the increased squamous cell carcinoma risk associated with ageing.

TABLE 2.

Mediators of Inflammaging in the Skin and their Respective Pathways

Inflammatory Factor	Type	Pathway and Potential Skin Damage	References
Reactive Oxygen Species (ROS)	Prooxidant	Cause skin cell damage; generate oxidized lipids; induce MMP expression in dermal fibroblast	19–22
TNF-alpha, IL-1	Primary pro-inflammatory cytokines	Initiate inflammatory responses in skin; induce the synthesis and release of other pro- inflammatory cytokines	23–27
IL-6, IL-8	Other pro-inflammatory cytokines	Initiate inflammatory responses in skin; induce the synthesis and release of other pro- inflammatory cytokines	21,28
Neutrophils	Immune Cell	Release elastase and MMPs that cause ECM degradation	21,29,30
Matrix Metalloproteinases (MMPs)	Enzyme	Cause ECM degradation, thus cause damage to dermis connective tissue and skin aging	21,31
Complement System	Innate Immune System	Activate macrophage; induced by UV and deposits on dermal-epidermal junction	32,33
Macrophages	Immune Cell	Infiltrate skin after UV-exposure; generate ROS and MMPs that cause ECM degradation	32,34,35

macrophages as illustrated in Figure 1. Zhuang et al published a comprehensive table of mediators of inflammaging in the skin; a modified version of this table can be found in Table 2.

Interestingly, it has been shown that the gastrointestinal tract's microbiome plays a central role in inflammaging and metaflammation as it's at the intersection of diet, metabolism, and innate immune response. Thus, the gut microbiome has far reaching effects. It regulates things like the circadian rhythm and sleep patterns through the production of melatonin as well as influences cardiovascular health. In fact, a healthy gut microbiome may even be protective and is associated with healthy aging and longevity.[36-39]

The effects of the cutaneous microbiome on systemic health has been less researched; although, like the gut, it may have the potential to influence overall health. The cutaneous microbiome is vast, and each square centimeter is home to several million microbes.[40] The role of the skin's microbiome in common dermatologic diseases like atopic dermatitis and psoriasis has been well elucidated. We know that restoring a healthy microbiome in atopic patients reduces the risk of flares and secondary infections[41-43] and that in psoriasis a decrease in the diversity of the skin flora increases the risk of flares and arthritis.[44,45] These conditions have also been noted to result in increased levels of pro-inflammatory cytokines, which can have serious systemic sequalae such as the increase in cardiovascular risk seen in psoriatic patients.[41,46-49]

One of the most interesting recent studies regarding the role of inflammaging in dermatology examines how a healthy skin barrier may systemically reduce inflammation.[50] Increased levels of inflammatory cytokines in the elderly have been linked to the development of age-related chronic disorders. In mice models, epidermal dysfunction in aged mice has been linked to elevated cytokine levels systemically. Interestingly, in these mice models, improving epidermal function reduced systemic cytokine levels.[51] Ye et al studied the effect of daily application of a barrier cream on cytokine levels in older adults. The active group (adults over 65, n=33) applied 3mL of a ceramide-based emollient topically twice-daily for 30 days. The control groups (adults over 65, n=25, adults under 30, n=11) used no topical skincare during the trial. Changes in epidermal function and levels of three key, age- related, plasma cytokines were measured at baseline and after treatment.

The researchers focused on IL-1β, IL-6, and TNF-α because they are considered primary biomarkers of inflammaging.[4] As expected, at baseline, the cytokines were elevated in the aged population vs younger cohort. Topical application of the barrier repair emollient significantly enhanced epidermal barrier function and stratum corneum hydration as measured by a multifunctional skin physiology monitor (MPA5; Courage–Khazaka Electronic GmbH). At the end of 30 days, IL-1β and IL-6 normalized, and TNF-α levels declined substantially in the active treatment group. In the control group over 65 and the younger cohort, there was no significant change in IL-1β, IL-6, and TNF-α. This study is interesting because it is one of the first clinical trials to show how skin barrier dysfunction may contribute to systemic inflammaging.

CONCLUSION

Research in aging-related inflammation is an emerging field.[5,52] Growing research suggests that reduction in systemic inflammation or inflammaging may directly correlate with a reduction in the risk of developing age-related diseases including

cancer.[1,38,39,53,54] Interestingly, there is proportionally less research on inflammaging as it relates to dermatology although it appears the skin may play a critical role. Dermatologists should be aware of inflammaging and the skin's role in this important aspect of aging. Further research is needed to elucidate the role of skin in inflammaging.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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