

Inflammation and Aging: The Skin Inflammasome in the Context of Longevity Science

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Abstract

The skin inflammasome is a critical component of the immune system, pivotal not only in responding to acute threats but also in contributing to the chronic inflammation associated with aging. This review provides an in-depth examination of the molecular mechanisms of the skin inflammasome, detailing its role in dermatological conditions like acne, atopic dermatitis, psoriasis, and hyperpigmentation, as well as its impact on systemic aging. We explore how longevity science is now focusing on these pathways to enhance skin resilience and potentially extend human health span. This involves innovative approaches such as drug repurposing, understanding the modulation of skin inflammation, and recognizing the systemic health reflections through the gut-skin axis.

Keywords: Classical immunology, Clinical immunology, Dermatology, Immune cells and organs, Immunomodulation, Immunotherapy, Inflammasome, Longevity, Longevity Science, Skin

Introduction

Inflammation is integral to the skin's defensive strategy, essential for wound repair and the elimination of pathogens. However, when inflammation becomes dysregulated, it can lead to chronic health issues and accelerate aging. The NLRP3 inflammasome in the skin acts as a sentinel, capable of detecting both external pathogens and internal cellular stress. Longevity science seeks to extend not only lifespan but also health span, defined as the period of life spent in good health, free from chronic diseases and disabilities associated with aging. Central to this endeavor is understanding how aging interacts with inflammasome pathways. With advancing age, the regulation of these pathways becomes impaired, leading to heightened basal activation of the inflammasome. This contributes to persistent low-grade inflammation, known as inflammaging, which accelerates aging processes and predisposes individuals to age-related diseases. This review aims to dissect the intricate connections between the skin inflammasome, aging, and longevity, compiling recent research to propose novel therapeutic strategies.

Inflammaging: The Chronic Inflammation of Aging

The term "inflammaging" describes the chronic, low-grade inflammation that drives aging. This review explores this concept, detailing how inflammasomes facilitate this process. We discuss how skin cells, including keratinocytes and macrophages, harbor inflammasome components, and how these systems transition from beneficial to detrimental as we age:

Inflammaging and aging biomarkers

The link between inflammaging, telomere shortening, epigenetic alterations, and mitochondrial dysfunction has been solidified, indicating that inflammasome activity contributes to systemic aging processes [7,20]. Recent studies suggest that the inflammasome's role in aging might be mediated by its response to cellular damage and stress, influencing the aging trajectory at a molecular level.

Cellular senescence

Senescent cells contribute significantly to inflammaging by

releasing SASP, a cocktail of inflammatory cytokines including IL-1 β , which can stimulate nearby inflammasomes, thus perpetuating inflammation and aging [8,26]. This not only affects the local environment of the skin but also has systemic implications.

Nad+ decline

With age, the decline in NAD⁺ levels is associated with mitochondrial dysfunction, which is a known activator of the NLRP3 inflammasome, thereby linking metabolic health directly to the inflammatory processes of aging [9,27]. This relationship underscores the potential of NAD⁺ supplementation in aging research.

The Skin Inflammasome: Molecular Mechanisms and Pathways

Nlrp3 inflammasome activation

Priming: The process begins with the upregulation of NLRP3 in response to signals like LPS from bacteria or endogenous danger signals such as ATP or uric acid. The transcription factor NF- κ B not only increases NLRP3 expression but also initiates the transcription of pro-IL-1 β , preparing the cell for an inflammatory response. This priming phase is crucial for sensitizing cells to subsequent activation signals, a mechanism that parallels arming a defense system [1,2]. Additionally, recent research has shown that other signaling pathways, including those mediated by DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns), can also prime the inflammasome [20].

Activation: Following priming, the inflammasome requires a secondary signal, often from cellular stress like ion flux, mitochondrial damage, or lysosomal rupture, to activate. Here, NLRP3 polymerizes with ASC and caspase-1, leading to the cleavage of pro-inflammatory cytokines into their active forms, IL-1 β and IL-18, initiating an inflammatory cascade. This dual-signal requirement is evolutionary, ensuring that activation occurs only under appropriate conditions, thus preventing unnecessary inflammation [2,3,21]. The involvement of various ion channels, including the P2X7 receptor for ATP, has been highlighted as key in this activation step [2].

Inflammasome in skin pathology

Acne vulgaris: *Propionibacterium acnes* in the sebaceous glands activates the NLRP3 inflammasome through its bacterial products like lipases or direct interaction with immune cells. This leads to the formation of inflammatory lesions, indicating the microbiome's critical role in skin health [4,22]. Recent studies have also begun to explore how the skin's resident microbiome might influence inflammasome activity, suggesting potential therapeutic avenues through microbiome modulation.

Atopic dermatitis: Continuous exposure to allergens or irritants results in sustained inflammasome activation, where IL-1 β not only drives inflammation but also compromises the skin barrier, perpetuating a cycle of 'itch-scratch'. This cycle not only aggravates barrier function but also promotes further inflammation, illustrating the complex feedback between skin barrier integrity and inflammasome activity [5,23]. The role of IL-33, another inflammasome-related cytokine, has also been implicated in the chronic nature of this condition.

Psoriasis: The NLRP3 inflammasome plays a central role in psoriatic lesions where IL-1 β sustains a feedback loop with IL-17 and IL-23, leading to keratinocyte proliferation and plaque formation. The persistent activation of this inflammasome highlights its potential as a therapeutic target, where blocking specific steps in this pathway could alleviate symptoms [6,24]. Recent advances in understanding the genetic basis of psoriasis suggest that certain genetic variants might predispose individuals to exaggerated inflammasome responses.

Hyperpigmentation: While not directly driven by inflammasomes, chronic inflammation can influence melanocytes through cytokines like IL-6, leading to melanin overproduction and pigmentation changes. This indirect link between inflammation and skin pigmentation underscores how inflammatory processes can have cosmetic as well as health implications [7]. The role of inflammasome activation in conditions like melasma is an area of growing interest.

Aging and inflammaging

Increased basal activation: The cumulative effect of UV radiation, oxidative stress, and environmental pollutants over a lifetime leads to a higher baseline of inflammasome activity. This contributes to the concept of 'inflammaging', where persistent low-grade inflammation hastens aging processes, particularly in the skin [8,25]. Recent findings also link this increased activation to the accumulation of cellular debris and senescent cells, further exacerbating the aging process.

Senescent cells: These cells, unable to proliferate, secrete SASP, which includes cytokines like IL-1 β that stimulate inflammasome activation in neighboring cells, thus perpetuating inflammation. This phenomenon not only affects local skin aging but has systemic repercussions, suggesting that targeting senescent cells could be beneficial for both skin and overall health [9,26].

Nad+ decline: As NAD⁺ levels fall with age, this impacts cellular energy and repair mechanisms, leading to mitochondrial dysfunction, which is a significant activator of the NLRP3 inflammasome. This connection between metabolic health and inflammation underscores the importance of metabolic interventions in aging research [10,27]. The potential of NAD⁺ precursors like NMN to reverse these effects is under active investigation.

Longevity Science and Skin Health

Nad+ and sirtuins

Nad+ boosting: Therapies aimed at increasing NAD+ levels, such as NMN or NR supplementation, are being explored for their potential to enhance DNA repair, improve mitochondrial function, and thereby reduce inflammasome activity, offering a novel approach to aging [10]. Clinical trials are underway to translate these preclinical benefits to human health.

Sirtuins: SIRT1, an NAD+-dependent protein, has shown anti-inflammatory effects that could mimic the longevity benefits of caloric restriction. Its ability to modulate inflammatory pathways might provide a pathway to reduce skin aging and inflammation [11,27]. Recent studies have also linked SIRT1 to the regulation of skin's immune responses, suggesting broader implications for skin health.

Senolytics

Dasatinib and quercetin: These compounds selectively eliminate senescent cells, reducing the secretion of SASP and thus chronic inflammation. This strategy is being investigated for managing age-related skin conditions, potentially offering a new paradigm in dermatological treatment [12,28]. The combination's efficacy in animal models has been promising, though human trials are necessary to confirm these benefits.

Targeting SASP: Rather than eliminating senescent cells, research is also focusing on modulating SASP to control inflammation without the potential risks of broad immune suppression. This could be particularly beneficial for aging skin, promoting a healthier aging process [13].

Other longevity molecules

AMPK activators: Metformin, traditionally used for diabetes, has shown potential in inhibiting inflammasome assembly, linking metabolic health directly to inflammation control in aging. Its pleiotropic effects might extend beyond diabetes management to include anti-aging properties for the skin [14,29].

mTOR inhibitors: Rapamycin, known for its immunosuppressive properties, can modulate mTOR pathways, which are implicated in aging and inflammation. By lowering inflammatory responses, it might slow down aging processes, including those affecting the skin [15]. The use of rapamycin in topical formulations is thus being explored.

Longevity Science and the Gut-skin Axis

Microbiome influence

The gut microbiome's balance significantly influences systemic inflammation, which in turn can affect skin health. Dysbiosis leads to increased gut permeability, allowing LPS

and other microbial products to activate skin inflammasomes, suggesting that maintaining gut health might indirectly benefit the skin [18,32].

Leaky gut and systemic inflammation

Increased intestinal permeability results in systemic inflammation, which can activate skin inflammasomes, contributing to conditions like psoriasis or general skin aging. This relationship supports the use of prebiotics, probiotics, or dietary interventions to manage skin conditions through gut health [19].

Psycho-neuro-endocrine pathways

The gut influences systemic stress responses and hormone levels, which can exacerbate skin conditions by promoting inflammation or collagen degradation. Cortisol, for instance, from chronic stress, can compromise skin barrier function and immune response, accelerating skin aging [5,6,30].

Dietary influence

Diets rich in anti-inflammatory nutrients like omega-3 fatty acids, antioxidants, and fiber can support a balanced gut microbiome, potentially reducing systemic inflammation and benefiting skin health [7,31]. The Mediterranean diet, in particular, has been associated with lower levels of inflammatory markers.

Immunological linkage

The gut educates the immune system, which can modulate skin immunity. Dysbiosis can lead to an imbalance in cytokine production, exacerbating inflammatory skin conditions. This suggests that interventions aimed at restoring gut microbial balance could have therapeutic implications for skin health [9,10,32].

Specific evidence

Recent studies provide concrete evidence for the gut-skin axis. For example, a randomized controlled trial showed that supplementation with *Lactobacillus rhamnosus* improved skin barrier function and reduced inflammation in patients with atopic dermatitis [42]. Additionally, dietary interventions like the Mediterranean diet, rich in omega-3 fatty acids and antioxidants, have been linked to reduced systemic inflammation and improved skin health [43]. Regular physical exercise has also been shown to modulate immune responses and reduce inflammasome activation, potentially benefiting skin health [44].

Drug Repurposing and Systemic Health Implications

Metformin

Its anti-inflammatory properties are now being explored

for dermatological benefits, potentially modulating inflammasome activity in the skin. This could offer dual benefits in managing both metabolic disorders and signs of skin aging [16,33]. The Targeting Aging with Metformin (TAME) trial is investigating metformin's potential to delay age-related diseases, including those affecting the skin, providing a robust framework for its application in aging research [14].

Statins

Beyond cholesterol management, statins have anti-inflammatory effects that could inhibit inflammasome activation, providing a novel approach to treat inflammatory skin diseases [17]. Studies suggest statins may benefit conditions like psoriasis due to their anti-inflammatory properties, with ongoing research exploring their efficacy in dermatology [45]. Their role in skin health is still under investigation but shows promise.

Therapeutic Strategies

The dual role of the inflammasome in health and disease has led to the development of targeted therapies, such as biologics that block cytokines like IL-1 β in psoriasis, demonstrating how molecular insights into inflammasome biology can guide treatment [6,34].

Despite the promise of senolytics and NAD⁺ boosters, their use in dermatology faces challenges regarding safety, cost, and efficacy in human trials. It is crucial to temper expectations with the current state of research, highlighting the need for more comprehensive studies to validate these approaches [10,26].

Challenges and considerations

Translating these findings into clinical practice involves hurdles such as ensuring long-term safety and sustainability. Senolytics, while effective in preclinical models, may have off-target effects on healthy cells, and their long-term impact on tissue regeneration requires evaluation. NAD⁺ boosters need further study to determine optimal dosing and potential side effects. Drug repurposing and lifestyle interventions, though promising, face challenges like individual variability and adherence, necessitating robust clinical trials to establish their efficacy and safety in real-world settings.

Other Contributors to Skin Aging and Inflammation

Oxidative stress

Chronic exposure to ROS from environmental or internal sources leads to cellular damage, promoting inflammation and aging. While antioxidants can mitigate some damage, their direct impact on modulating inflammasome activity is still under investigation [7,35].

Mitochondrial dysfunction

Mitochondria's role in energy production and inflammasome activation means that their dysfunction with age can increase ROS, triggering NLRP3 inflammasome activation, directly linking metabolic health to skin aging [8,36].

External factors

UV radiation and pollution not only damage DNA but also disrupts the skin barrier, allowing for increased inflammasome activation by environmental agents. Research into protective mechanisms against these factors is vital for preventing skin aging and inflammation [7,37].

Actionable Insights for Translational Research

Personalized therapies

The future of dermatological treatment lies in personalizing strategies based on individual inflammatory profiles, genetic predispositions, and lifestyle factors. This approach could optimize treatment outcomes while minimizing side effects [38]. However, practical implementation faces challenges such as the high cost of genetic profiling and the need for large-scale validation studies.

Systemic interventions

Exploring how systemic health interventions like diet, exercise, or microbiome modulation can influence skin inflammasome activity might lead to innovative therapeutic strategies [39].

Topical treatments

There is a demand for less invasive, more effective topical agents that can target inflammasome pathways directly. Advances in drug delivery systems, like nanoparticles, could revolutionize this field [40].

Biomarkers and monitoring

Identifying reliable biomarkers for inflammasome activity in the skin would enhance our ability to monitor treatment efficacy and disease progression, bridging the gap between research and clinical application [41].

Conclusion

The skin inflammasome plays a pivotal role in both protective and pathological inflammation, making it a critical target for interventions aimed at extending health span. This review has synthesized current insights into how inflammasomes contribute to aging and skin disorders, highlighting the innovative approaches of longevity science to mitigate inflammation. The gut-skin axis underscores the

systemic nature of health, suggesting that interventions in one area might yield benefits elsewhere. By leveraging drug repurposing, personalized medicine, and lifestyle modifications, we can better manage aging. This review not only links dermatology with longevity science but also opens new research and therapeutic avenues, potentially reshaping our approach to aging and health maintenance. However, limitations exist, such as reliance on preclinical models and the need for more human studies to validate findings. Future research should address specific questions, such as the role of gut microbiota in skin inflammasome activation, the development of topical senolytics, and the integration of systemic and dermatological interventions.

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