Inflammasome Activation in Pollution-Induced Skin Conditions

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Summary: Exposure to air pollutants has been now associated with detrimental effects on a variety of organs, including the heart, lungs, GI tract, and brain. However, recently it has become clear that pollutant exposure can also promote the development/exacerbation of a variety of skin conditions, including premature aging, psoriasis, acne, and atopic dermatitis. Although the molecular mechanisms by which pollutant exposure results in these cutaneous pathological manifestations, it has been noticed that an inflammatory status is a common denominator of all those skin conditions. For this reason, recently, the activation of a cytosolic multiprotein complex involved in inflammatory responses (the inflammasome) that could promote the maturation of proinflammatory cytokines interleukin-1β and interleukin-18 has been hypothesized to play a key role in pollution-induced skin damage. In this review, we summarize and propose the cutaneous inflammasome as a novel target of pollutant exposure and the eventual usage of inflammasome inhibitor as new technologies to counteract pollution-induced skin damage. Possibly, the ability to inhibit the inflammasome activation could prevent cutaneous inflammaging and ameliorate the health and appearance of the skin. (*Plast. Reconstr. Surg.* 147: 15S, 2021.)

Air pollution consists of chemical, physical, or biological agents that can cause harmful effects on humans, animals, and plants.[1] Air pollutants originate from indoor and outdoor sources in developing and developed countries, making air pollution a worldwide concern.[2] The Environmental Protection Agency (EPA) has defined national ambient air quality standards for 6 common air pollutants or "criteria air pollutants," which include ground-level ozone (O_3), particulate matter (PM), carbon monoxide (CO), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2).[3] Interaction between air pollutants and sunlight can result in the formation of pro-oxidants, including O_3.[4,5] The major source of anthropogenic emissions of oxide gases and PM is the combustion of fossil fuels from stationary sources and motor vehicles.[4,6] PM is a mixture of liquid, solid, or liquid and solid particles suspended in air that is composed of organic, such as polycyclic aromatic hydrocarbons (PAHs), and inorganic components, including transition metals. Based on diameter, PM can be divided into 3 categories: PM10 (<10 μm), PM2.5 (<2.5 μm), and ultrafine particles (<100 nm).[7,8] Environmental tobacco smoke is a complex mixture of thousands of chemicals coming from the burning of a cigarette and smoke exhaled from smokers; therefore, it represents a major contaminant of indoor air.[9,10]

Air pollution kills an estimated 7 million people worldwide every year; 9 out of 10 people breathe air containing high levels of pollutants.[11] The adverse health effects of exposure to air pollutants have been subjected to intense research in the last few decades.[12,13] Beyond the strong correlation to cardiovascular and respiratory diseases,[13] exposure to air pollutants is also involved in the development/exacerbation of numerous skin disorders.[14]

SKIN AS A PRIMARY TARGET OF AIR POLLUTION

The skin is composed of two main layers: the dermis and the epidermis. The dermis consists

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primarily of fibroblasts, which synthesize collagen and elastin. The epidermis is the outer, protective layer of the skin and consists of keratinocytes, which are organized into different layers, based on differentiation status. The skin is the primary interface between our body and the external environment. Thus, its most critical role is to provide a strong physiological barrier, which is mediated by the outermost layer of the epidermis, the stratum corneum. This layer consists of several packed layers of flattened dead cells, which are constantly shed and surrounded by an exterior lipid matrix to form a "brick and mortar" shield.[15] There are four pathways of skin penetration, including mechanical delivery, an intracellular route, a transcellular route, and a transfollicular route.[16,17] It has been suggested that toxins present on PM, such as PAHs, can enter systemic circulation through hair follicles or transepidermal absorption.[18–20] Common pollutants interacting with the skin are pro-oxidant compounds, such as O_3 and NOx, which initiate a cascade of oxidative damage, resulting, when there is a chronic exposure, in the development/exacerbation of various skin disorders.[21]

Some individuals may present a compromised skin barrier, due to intrinsic factors, including aging[22] or genetic predispositions,[23–25] or due to extrinsic factors, such as repeated exposure to external insults, leading to chronic diseases.[26,27] Impaired barrier function results in increased risk of absorption and penetration of air pollutants. Therefore, individuals with altered barrier function are particularly sensitive to pollution-induced skin disorders.[28]

MOLECULAR MECHANISMS INVOLVED IN POLLUTANT TOXICITY

Pollutant exposure results in the induction of an oxidative stress/inflammatory status in cutaneous tissues,[27] which is exacerbated when pollutants act synergistically.[29,30] However, the mechanism of action of single pollutants varies. For instance, O_3 does not penetrate the skin; it instantaneously interacts with lipids in the upper layers of the epithelium, generating a cascade of ozonation products that drive the production of reactive oxygen species (ROS) and aldehydes, such as 4-hydroxy-2-nonenal.[31–35] Other pollutants, such as PM and cigarette smoke, also alter skin redox homeostasis by inducing lipid peroxidation, albeit in different manners. For instance, particles have been suggested to eventually penetrate the skin, triggering ROS production and lipid peroxidation,[36–38] although this idea is controversial.[29] Transition metals in PM can undergo Fenton or Fenton-like chemistry, resulting in production of the hydroxyl radical.[39] Furthermore, PAHs can be converted into redox-active quinones that stimulate ROS production in keratinocytes.[39] Moreover, water-soluble PAHs of cigarette smoke increase NAPDH oxidase activity within skin, inducing oxidative stress.[40,41]

Therefore, the effects of these various stressors all result in increased ROS, which are key mediators of cellular signaling pathways,[42,43] inducing activation of redox-sensitive factors, such as proinflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein-1, Nrf2, and heat shock proteins.[44–47] Moreover, 4-hydroxy-2-nonenal, a product of lipid peroxidation, is able to interact with DNA and proteins,[48,49] forming adducts that damage DNA and alter protein conformations.[50–53] In skin, pollutant exposure results in inflammation, cellular apoptosis, and DNA and mitochondrial damage.[36–38] Increased oxidative stress in the skin also stimulates activation of matrix metalloproteinases, which breakdown collagen and elastin, contributing to skin aging.[54] Indeed, the involvement of pollutant exposure in skin aging is believed to be due to pollutant-induced activation of the aryl hydrocarbon receptor (AhR), promoting skin inflammaging.[55–61] Thus, it is no surprise that both inflammation and oxidative stress are displayed in several skin conditions,[62–64] and cross-talk between these two conditions results in skin inflammaging.[65–69]

SKIN CONDITIONS RELATED TO POLLUTION

Exposure of skin to air pollutants alters the functions of epidermal proteins and damages lipids and DNA, leading to a range of skin disorders.[70] The most prevalent skin disease associated with failure of the skin barrier is atopic dermatitis (AD); defects in barrier function can lead to increased vulnerability to air pollutants.[71] A large range of environmental stressors are involved in the development or aggravation of AD, such as environmental tobacco smoke, volatile organic compounds, nitrogen dioxide, and PM.[72–76] There is clear evidence that individuals living in urban areas with higher exposure to vehicle exhaust are more likely to develop AD.[77–80] Furthermore, childhood exposure to environmental tobacco smoke is a major risk factor for AD.[81] In addition, O_3 exposure has been correlated with urticaria, AD, and contact dermatitis.[82]

Skin exposure to environmental stressors is also associated with the development/exacerbation of psoriasis, aging, cancer, and acne. For instance, tobacco smoke is an independent risk factor for psoriasis development.[83,84] PM is one of the main pollutants that contributes to extrinsic skin aging, based on cohort studies using the SCINEXA aging score.[85] Characteristics of aging, such as wrinkles and pigmented spots, are more frequently observed in subjects living in urban areas.[85] Premature skin aging is also observed in smokers, independently of age, sex, and sun exposure, which is known as "smoker's face."[86,87] Additionally, PM contains PAHs, which are involved in the development of skin cancer.[5,7,88,89] Other studies have demonstrated a link between acne vulgaris and air pollution.[90,91] Exposure to PAHs can lead to acneiform eruptions and chloracne.[92] Some studies have also shown a correlation between acne severity and the number of smoked cigarettes.[93,94] In addition, cigarette smoke has been associated with androgenetic alopecia.[95] In conclusion, exposure to environmental stressors contributes to the development/exacerbation of inflammatory skin diseases and premature aging.

INFLAMMASOME AND SKIN

Inflammasomes are cytosolic multiprotein oligomer complexes of the innate immune system.[96] Activation of these complexes is responsible for the release of inflammatory cytokines, including interleukin (IL)-1β and IL-18, which protects against harmful stimuli (infectious pathogens, irritants, dead cells), by modulating immune responses in various tissues.[97] These complexes are composed of a pattern recognition receptor sensor, which recognizes pathogen-associated molecular patterns or danger-associated molecular patterns released by dead cells,[98] the speck-like receptor protein ASC, and the enzyme caspase 1. Upon stimuli recognition, ASC complexes with the pattern recognition receptor and oligomerizes, forming a complex scaffold and interacting with pro-caspase 1, promoting its maturation.[99] Once activated, caspase 1 can cleave pro-IL1β and IL-18 into their active forms, initiating inflammation or even causing a type of cell death termed pyroptosis.[100–102] Excessive production of IL-1β and IL-18 is associated with a variety of autoinflammatory and autoimmune diseases, thus these cytokines are crucial mediators of local and systemic inflammation.[103–105]

Several studies have demonstrated that inflammasome activation is involved in the onset of autoinflammatory diseases, neurologic pathologies, and metabolic disorders.[106–108] Importantly, inflammasome activation has also been implicated in the development/exacerbation of skin inflammatory pathologies.[109,110] The most well-characterized inflammasomes belong to the Nod-like receptor (NLR) and Aim2-like receptor families, such as NLRP1, NLRP3, NLRC4, and AIM2, which are mainly present in immune cells, although they are also found in keratinocytes.[111–113] These receptors all display a similar mechanism of activation and are induced by a variety of stimuli, including LPS, ATP, cytosolic DNA, ROS, and pathogens.[114] Several studies have also demonstrated that pollutants are able to induce inflammasome activation. For instance, several cardio-pulmonary diseases have been shown to be associated with NLRP3 inflammasome modulation by particulate matter,[115–120] cigarette smoke,[121,122] and O_3.[123–125] However, although skin is constantly exposed to environmental stressors, very few studies have demonstrated whether pollutant exposure triggers inflammasome activation in skin. Thus, only the role of UV light has been appreciated; activation of NLRP1, NLRP3, AIM2, and NLRC4 inflammasomes can be induced by UVB exposure in human keratinocytes.[126–130] A recent study also demonstrated that the NLRP1 inflammasome can be activated by O_3 exposure in different human skin models via redox regulation.[131] Thus, environmental stressors may promote the development/exacerbation of skin conditions by inducing inflammasome activation, and opening a new area of research in preventing stressor-induced skin damage and inflammation (Fig. 1).

INFLAMMASOME AND SKIN PATHOLOGIES

Dysregulation of inflammasome-associated cytokines, such as IL-1 beta and IL-18, is known to induce excessive immune cell infiltration and perpetuates skin inflammation, leading to the onset of several skin disorders, such as Cryopyrin-Associated Periodic Syndrome, familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease.[132–134] In recent years, other skin pathologies that display an altered production of interleukins, such as acne, psoriasis, and atopic dermatitis, have also been correlated with altered inflammasome activity.[135–143] Indeed, several studies have demonstrated that high levels of both IL-1β and inflammatory caspases, which are known to be modulated by inflammasomes,[144] are found

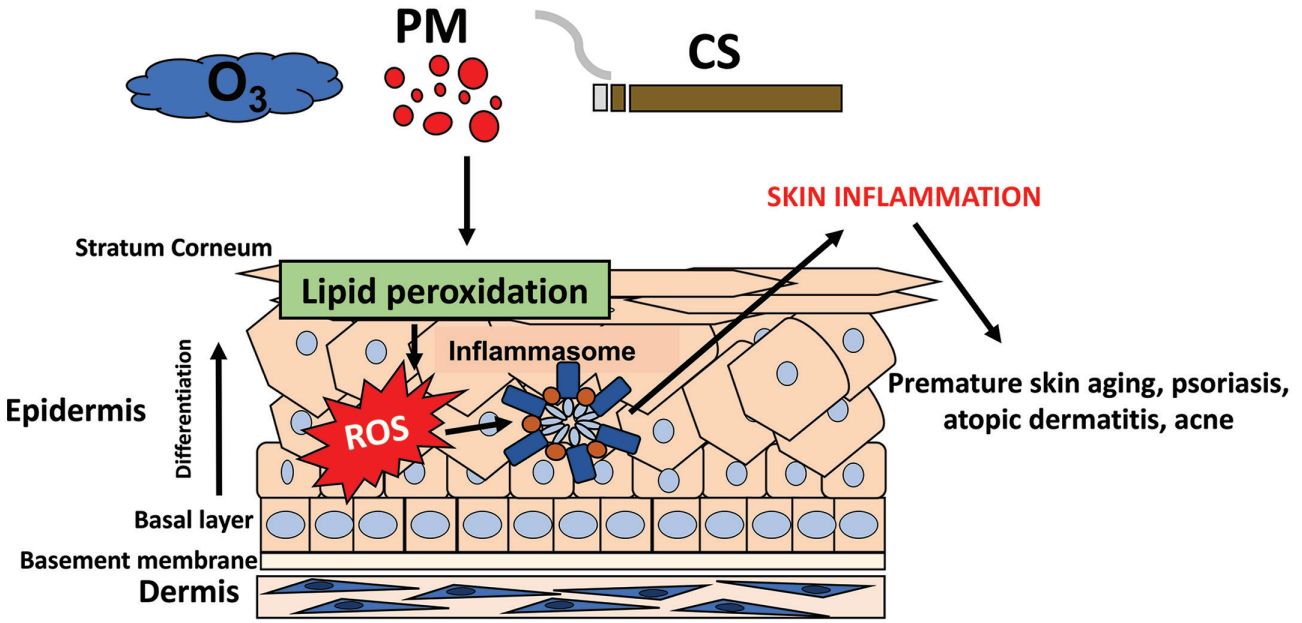

Fig. 1. Exposure to environmental stressors and inflammasome activation. Exposure of the skin to ozone (O_3), cigarette smoke (*CS*), and particulate matter (*PM*) induces lipid peroxidation (i.e., production of 4-hydroxynonenal) and production of reactive oxygen species (*ROS*), which can stimulate inflammasome activation. Stressor-induced activation of the inflammasome results in skin inflammation, leading to the development/exacerbation of a variety of skin conditions, including premature aging, psoriasis, atopic dermatitis, and acne.

in psoriatic and dermatitis murine models,[145,146] as well as in human psoriatic skin explants.[147,148] Higher levels of AIM2 inflammasomes, induced by cytosolic DNA, have been found in human keratinocytes of psoriatic lesions, which can be suppressed by binding of the antimicrobial peptide LL-37 to cytosolic DNA.[149,150] Mutations of the NLRP1 inflammasome have been associated with vitiligo, atopic dermatitis, psoriasis, cancer, and photoaging.[151–153] Moreover, a recent study demonstrated that the high levels of IL-1β associated with the development of a Th17 micro-milieu, displayed in several autoinflammatory diseases (like psoriasis and atopic dermatitis), were induced by activation of the NLRP1 inflammasome via caspase-5 maturation.[154] Single-nucleotide polymorphisms in NLRP1 have also been associated with a higher susceptibility to psoriasis[155] and non-segmental vitiligo in humans.[156] Other studies have investigated the role of NLRP3 in different skin pathologies and have found that altered expression of NLRP3 is associated with psoriasis and atopic dermatitis in humans and mice.[157,158] In addition, inhibition of the NLRP3 inflammasome via metformin in human keratinocytes can actually prevent caspase 1 maturation and consequent IL-1β production, ameliorating psoriatic symptoms.[159] Moreover, *Propionibacterium acnes*, which plays a pivotal role in acne development, has been shown to activate NLRP3 in acne lesions.[160–162] Multiple studies have demonstrated that higher levels of NLRP3-induced caspase 1 and IL-1β can be prevented by several compounds in different models of acne.[163,164] Finally, since skin aging is associated with systemic inflammation and oxidative stress, mainly due to the activities of environmental stressors,[165,166] different studies have demonstrated that excessive inflammasome activity can lead to the onset of premature aging, particularly in the case of UV exposure,[167,168] which can also cause photodamage and skin cancer.[169,170]

INFLAMMASOME AS A NEW TARGET FOR PREVENTING POLLUTION-INDUCED SKIN DAMAGE

Currently, many inflammasome inhibitors have been investigated as treatments for inflammatory diseases. Some of these inhibitors directly target NLRP3,[171] by modifying cysteines, binding to the NLRP3 NACHT domain, or inhibiting the ATPase activity of NLRP3.[172–174] MCC950 is an NLRP3 inflammasome-selective inhibitor that blocks canonical and non-canonical NLRP3-induced ASC oligomerization in mice *in vivo* and in human cells *in vitro*.[175] MCC950 reduces skin inflammation in mice with allergic dermatitis and Cryopyrin-Associated Periodic Syndrome[175] and

prevents dermal inflammation.[176] Recently, BAY 11-7082 was proposed as a promising treatment for psoriasis-like dermatitis, based on its ability to dually inhibit both NF-κB and NLRP3.[177]

An alternative way to inhibit inflammasome activation is by targeting inflammasome-associated proteins or the non-canonical inflammasome pathway. Drugs targeting downstream mediators, such as caspase-1 or IL-1β, have demonstrated therapeutic action in many inflammation-associated diseases.[178–180] For example, anakinra, an IL-1R antagonist, has been used for treating melanoma.[181] Canakinumab, an IL-1β-specific monoclonal antibody, has been used in patients with Cryopyrin-Associated Periodic Syndrome[182]; Ac-YVAD-CHO, an inhibitor of caspases, is currently under investigation for treating psoriasis.[145,183] The main drawback of using these inhibitors is that they may cause systemic immune suppression.[184] Moreover, some caspase inhibitors cause hepatoxicity.[185] However, some drugs initially used to treat diabetes, such as glyburide and metformin, have shown potential *in vitro* and *in vivo* in treating skin diseases by preventing NLRP3 inflammasome activation.[159,186,187] Furthermore, endogenous molecules such as the cathelicidin LL-37, superoxide dismutase-3, and dietary omega-3 fatty acids have been shown to suppress inflammasome-related skin pathologies.[157,188,189] However, most of the existing data on inflammasome inhibition comes from *in vitro* or *in vivo* experiments in animal models, and these studies have primarily focused only on targeting the NLRP3 inflammasome. Future studies should focus on whether targeting other types of skin-associated inflammasomes, such as NLRP1 or Aim2, can prevent the development/exacerbation of inflammatory skin disorders.[153,190–192] In addition, it would be interesting to test whether targeting multiple types of inflammasomes ameliorates inflammatory skin conditions, since it is likely that multiple types of inflammasomes are activated in these skin disorders simultaneously.[193]

Moreover, medicinal phytocompounds (including aloe vera, resveratrol, and curcumin) have been characterized as potent inhibitors of NLRP3 inflammasome-mediated IL-1βproduction *in vitro* and *in vivo*.[126,193–199] Some antioxidant topical treatments have shown beneficial effects in targeting the inflammasome for treating psoriasis and *P. Acnes* infection in human skin explants and murine models.[163,164,200–204] Despite demonstrated therapeutic effects in reducing inflammation, utilizing polyphenols as therapeutics is limited by the fact that the bioavailability of these compounds is very variable.

Another caveat in targeting the inflammasome to prevent the development/exacerbation of stressor-associated skin conditions is whether inhibitors should be applied systemically, topically, or in combination. Systemic administration of inflammasome inhibitors has demonstrated efficiency in preventing several inflammasome-associated diseases, including Alzheimer's disease and multiple sclerosis.[184] Topical application to treat skin diseases could prevent systemic immune suppression, depending on penetration into the skin, although topical application may also limit the efficacy of these drugs, since inflammasome activation in infiltrating immune cells and underlying fibroblasts likely contributes to the development/exacerbation of the aforementioned skin conditions. Moreover, systemic application via ingestion may simultaneously prevent the development/exacerbation of other pathologies associated with inflammasome activation, such as Alzheimer's and cardiovascular disease.

CONCLUSIONS

Overall, the inflammasome should be investigated as a target to prevent the development/exacerbation of stressor-associated skin conditions, including atopic dermatitis, psoriasis, acne, and premature aging. Although numerous strategies to target the inflammasome have been explored, none of these studies have investigated the efficacy of preventing stressor-induced skin damage and inflammation by inhibiting inflammasome activation. Moreover, different modes of application, such as systemic and topical, should be explored to determine the most effective route of administration. It is possible that targeting the inflammasome machinery would result in improving skin health and postponing the extrinsic cutaneous inflammaging.

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