

# Chronic inflammation is etiology of extrinsic aging

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## Summary

Skin care regimens using active ingredients that are recommended by physicians who treat mucocutaneous conditions including aging should become more focused on reversing and preventing chronic inflammation. This adjustment of therapeutic and preventive strategies is necessary because chronic inflammation appears strongly linked to many preventable and treatable skin diseases and conditions such as visible skin aging. Mucocutaneous inflammation as the final common pathway of many systemic and mucocutaneous diseases including extrinsic aging has been established at the molecular and cellular levels. The corollary to this strategy includes inhibition of primary activators of mucocutaneous inflammation such as stratum corneum permeability barrier disruption, blocking any pro-inflammatory environmental insult such as ultraviolet radiation, and quenching tissue responses to these insults. This review will present the scientific rationale substantiating the conclusion that chronic inflammation is the common denominator in many mucocutaneous pathophysiologic processes including extrinsic skin aging.

*Keywords:* aging face, anti-aging products, anti-inflammatory

## Inflammation linked to diseases

Denham Harmon first documented cellular destruction by reactive oxygen species (ROS) and the resultant activation of inflammatory cascades over 50 years ago.<sup>1</sup> Lavker and Kligman then documented inflammation as an etiology of extrinsic skin aging about two decades ago.<sup>2</sup> In his book, *The Wrinkle Cure*, Perricone brought inflammation-induced damage of the skin into the public eye. He stated that visible skin aging can be reduced and/or prevented by daily use of cosmeceuticals containing antioxidant and/or anti-inflammatory active components, coupled with a diet rich in antioxidant and/or anti-inflammatory foods.<sup>1</sup> Articles published in several major lay magazines in the past several years have further exposed the public to the concept that the development of inflammation of skin and other organs are critical events

in the development of diseases, cancers, and aging. Wellness guru Andrew Weil has published his anti-inflammatory diet because he believes that “without question, diet influences inflammation.”<sup>3</sup> He and other researchers state, “the surprising link between inflammation and heart attack, colon, esophageal, prostate and skin cancer, Alzheimer’s disease, stroke, multiple sclerosis, rheumatic fever, rheumatoid arthritis, type I diabetes mellitus, systemic lupus erythematosus and scleroderma as well as aging strongly suggests a single inflammation-reducing remedy would effectively treat and prevent humans’ major debilitating and fatal conditions. This radically changes the medical community’s concept of disease therapy.”<sup>3–5</sup>

## Mucocutaneous inflammation – disease link

The concept of preventing and reversing chronic inflammation as treatment, prevention, and/or control of disease must also be applied to mucocutaneous surfaces, the first site of interface between the xerotic terrestrial

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environment and aqueous internal environment of the organism. These tissues are exposed to numerous pro-oxidant and pro-inflammatory insults; thus, mucocutaneous cells should be expected to benefit from direct exposure to antioxidant and/or anti-inflammatory treatment and prophylactic active compounds. All antioxidants have anti-inflammatory effect. The converse is not true because there are other pro-inflammatory mechanistic pathways not modulated by antioxidants that up-regulate destructive matrix metalloproteinases (MMPs). Aspirin, diclofenac, and indomethacin are useful topical and orally administered anti-inflammatory agents but are not antioxidants. Indomethacin has been documented to reverse photo-aging – induced wrinkling in a murine model with topical application.<sup>6</sup>

The major source of ROS in the skin and all human tissues is from normal cellular respiration and metabolism. The acute reaction by these ROS includes polymorphonuclear leukocytes infiltration that subsides within 10 to 14 days after injury. Continued insult as shown by Nicholoff and Naidu results in a shift to a lymphohistiocytic infiltrate and markedly up-regulated MMP synthesis. Tissue and cellular destruction and anomalous repair of collagen, elastin, and ground substance follows. In the case of extrinsic aging, MMPs induce micro scars, which clinically manifest as fine lines and wrinkles. Non-melanoma skin cancer also results from these chronic inflammatory cascades.<sup>7</sup>

Elias and Feingold demonstrated that disruption of the stratum corneum barrier not only is characteristic of many chronic inflammatory diseases but induces inflammation itself. These diseases include contact, atopic and seborrheic dermatitis, extrinsic aging, and certain disorders of cornification and papulosquamous diseases such as psoriasis and lichen planus.<sup>8</sup>

The incidence of chronic inflammatory skin diseases appears to be significantly increasing in all age groups. Approximately 15% to 30% of American children are afflicted by eczematous dermatitis. Occupational contact dermatitis has become the leading cause of lost days of work in America and worldwide. In 2004, 39% of all American adults were reported to suffer with a chronic inflammatory skin condition lasting longer than 1 month during their lifetime.<sup>9</sup>

Rudolf Virchow a century and a half ago suggested cancer developed at sites of inflammation.<sup>4</sup> In the last decade, it has become widely accepted that inflammation and mutation mutually reinforce malignant deterioration of a variety of cell types.

Mucocutaneous malignancies have reached epidemic proportions. During each of the past 3 years, over a million Americans were diagnosed with a skin cancer

requiring surgery. About 50% of people over 65 years old are afflicted with premalignant actinic keratoses. The most common procedures performed today by dermatologists relate to skin cancer therapy. Surgical and destructive procedures for skin cancer rose by 12% to over 1.7 million despite massive public and medical education on the relationship of sunlight to skin cancer.<sup>10</sup> This trend is increasing despite the introduction in the 1980s of sunscreens with a sun protection factor of 15 or greater, and broadening the radiation spectrum of protection to include ultraviolet A (UVA) exposure.

During this same period, however, the popularity of exfoliating strategies with alpha hydroxy acids (AHAs), retinoids, and microdermabrasion has exploded. The number of estheticians and spas, including those types of practices owned by physicians, that perform exfoliating procedures has also grown rapidly.

Mild barrier disruption of any cause like suberythematous doses of UV light induce occult but destructive chronic inflammation.<sup>11</sup> Any degree of repeated or chronic disruption of the stratum corneum barrier has been documented to activate chronic inflammation.<sup>8</sup> Acute inflammation followed by complete rejuvenation of the stratum corneum permeability barrier does not seem to induce or exacerbate destructive chronic inflammation if more than 2 weeks elapses between treatments.

Chronic inflammation that is induced by both AHAs and retinoids seems to be primarily the result of barrier disruption. The U. S. Food and Drug Administration (FDA) in 2000 developed a warning for AHA products with a concentration over 10% and pH under 3.0 due to increased photosensitivity and premalignant deterioration of keratinocytes. Because the AHAs are not photosensitizers, unlike retinoids, the photoreactivity must be attributed to exfoliation of the barrier. Halliday as well as others report increased cutaneous malignancies with prolonged topical retinoid use.<sup>12</sup> These results are controversial as short-term topical retinoid use is documented to reduce cutaneous malignancies in several animal species and clinical observations in humans.<sup>13</sup>

The correlation of the rising skin cancer epidemic with increasing exfoliative strategies forces skin care professionals to consider whether chronic inflammation induced by stratum corneum permeability barrier disruption plays a contributing role. It has long been known that wound care with occlusive dressings and ointments accelerates wound healing. Moreover, the FDA has established an over the counter monograph for skin protectant drugs, which includes petrolatum, glycerine, and allantoin. This author and Elias established that a lipid mixture of ceramides, cholesterol, and free fatty acid applied topically effectively reversed compromised permeability barrier function.

## Anti-inflammatory therapy impacts aging

Methotrexate and corticosteroids are major allopathic therapies for treating psoriasis, dermatitis, cutaneous T-cell lymphoma, and a variety of other inflammatory systemic diseases and malignancies, which strongly suggests a pathophysiologic link between inflammatory and neoplastic diseases. A nonsteroidal anti-inflammatory agent, diclofenac has received FDA approval to treat premalignant actinic keratosis with topical application. Systemic lupus erythematosus, dermatomyositis, and scleroderma are systemic diseases manifested by mucocutaneous abnormalities. Epidermal atrophy and irregular pigmentation, which are characteristic of these diseases, are also parameters of extrinsic aging.<sup>6</sup>

The success of certain alternative and complementary medicinal remedies for a wide spectrum of diseases, including cancer, supports the allopathic medical conclusion that inflammation is the final common pathway for many diseases. The public's use of alternative and complementary medicine surpassed the volume of allopathic outpatient medicine in 1995. Half of the top 10 selling herbs have documented anti-inflammatory and/or antioxidant mechanisms of action in humans and/or animals. More than 100 herbs are being marketed in topical nonprescription skin care products, including cosmeceuticals. Many of these have documented anti-inflammatory and/or antioxidant activity suggesting they may be beneficial in treating and/or preventing inflammatory diseases and extrinsic aging. There are more than 8000 documented antioxidant ingredients; yet, only 14 have been incorporated into topical formulations, which were documented in human clinical trials to reverse certain signs of extrinsic aging.<sup>14,15</sup>

Herbal ingredients with known antioxidant and/or anti-inflammatory activity now used in topical dermatological and cosmeceutical products for treatment of certain inflammatory conditions have been documented in double-blind clinical trials to significantly improve signs of extrinsic skin aging. These botanical extracts applied topically include fruits rich in AHAs, retinol, certain ascorbic acids formulations, soy milk and total soy,<sup>11</sup> date palm fruit as a solitary agent,<sup>16</sup> green tea (when also ingested),<sup>17</sup> colloidal oatmeal and oat,<sup>18,19</sup> arbutin,<sup>20</sup> and parthenolide free extract of feverfew,<sup>21</sup> and a proprietary formulation of date kernel, meadowfoam, and flax.

The top 10 selling herbs accounted for over \$1 billion in sales in 2004. Three oral supplements containing multiple herbal antioxidants and/or anti-inflammatory activity such as a pomegranate mix have been documented in double-blind clinical trials to effectively improve signs of extrinsic aging.<sup>22</sup> Oral products with individual

botanically derived ingredients have been documented in open and double-blind clinical trials to improve signs of extrinsic skin aging and include curcumin,<sup>20</sup> olive oil,<sup>23</sup> pycnogenol,<sup>20</sup> and polypodium leucotomas.<sup>24</sup> Green tea and pomegranate each demonstrated efficacy in open label trials when topical and oral administration were combined.<sup>17,22</sup>

Unfortunately, the paucity of safety and efficacy clinical trials of finished product for the majority of skin care products marketed today makes the selection of such products to recommend to patients somewhat of a challenge. A few products have been introduced by new companies that should become more prominent in the near future. It is intuitive that the most effective anti-inflammatory agent will most likely achieve therapeutic concentrations to block and reverse inflammation if directly applied to the tissue. This suggests topically applied products would be preferred. However, formulation stability and delivery of the active ingredients through the stratum corneum at therapeutic concentrations become major challenges, as suggested by Dr Pinnell, a world-renowned expert on antioxidants.<sup>25</sup>

## Molecular mechanisms

Environmental insults producing destructive ROS include smoking, pollution, harsh skin care regimens, medical and cosmetic procedures, preservatives, topical drug delivery recipients, irritants including certain prescription topical therapies, allergens, blistering, wounds, ultraviolet, and X radiation. The first correlation of inflammation and skin aging was described by Lavker and Kligman in 1988 when they reported a mononuclear leukocyte and mast cell infiltration closely apposing papillary dermal fibroblasts in photo-damaged skin.<sup>2</sup> The stratum corneum permeability barrier disruption is now known to activate epidermal keratinocytes to release preformed as well as up-regulate synthesis of multiple biologic response modifiers. Preformed tumor necrosis factor-alpha (TNF $\alpha$ ), interleukins 1 (IL-1) and 8 (IL-8), other pro-inflammatory cytokines, chemokines and ions, released upon barrier disruption are the immediate first step to trigger protective acute inflammation.<sup>7,26</sup> Up-regulation of stratum corneum lipid synthesis and keratinocyte proliferation later ensues to repair the compromised permeability barrier.<sup>8</sup>

The binding of epidermal TNF $\alpha$  and IL-1 to their receptors and activation of kinase pathways induce the inflammatory cascades by translocating the two nuclear receptors, activating protein (AP-1) and nuclear factor kappa beta (NF $\kappa$ B) into the nucleus. Synthesis of a variety of transcription factors including IL-8, intracellular

activating macrophage factor (ICAM-1), defensins, E-selectins, transforming growth factor-beta (TGF $\beta$ ), and prostaglandin E<sub>2</sub> (PG-E<sub>2</sub>) are all up-regulated. These gene products result in chemotaxis of inflammatory cell infiltrates among other pro-inflammatory activities.<sup>26,27</sup>

MMPs are zinc-dependent enzymes involved in degradation and remodeling of matrix ground substance, collagen, and elastin. These destructive enzymes are synthesized in fibroblasts, keratinocytes, mast cells, macrophages, and T lymphocytes. Collagenase (MMP-1), stromelysin (MMP-3), and gelatinase (MMP-9) are the most important. The signs of extrinsic skin aging such as fine lines, wrinkles, fragility, and laxity are due to solar elastosis, collagen destruction and tissue atrophy induced by destructive MMP activity. Not only do they play important roles in inflammation, tissue catabolism, and remodeling, the MMP-induced chronic inflammation triggers a cascade resulting in malignant deterioration of mucocutaneous cells.<sup>27</sup>

### Future strategy

It follows that preventing and reversing chronic inflammation should be a primary strategy of physicians who treat and prevent mucocutaneous diseases, aging, and cancer. The ideal regimen would consist of skin care products with anti-inflammatory and/or antioxidant effects applied topically, coupled with products which optimize the stratum corneum permeability barrier. The broadest spectrum regimen would also include a diet and possibly oral supplements rich in anti-inflammatory and/or antioxidant ingredients. Use of exfoliating procedures should always be followed immediately by barrier repairing formulations consisting of ceramides, cholesterol, and free fatty acid. Moreover, consistent use of AHAs and retinoids should be augmented with regular use of a cosmetically elegant formulation with anti-inflammatory/barrier optimizing properties. These strategies should be expected to maximize and maintain the protective function and structure of the mucocutaneous surfaces.

### Summary

The linking of chronic inflammation to multiple cutaneous and systemic diseases, including malignancies and skin aging, was first suggested over a century ago. The cellular and molecular mechanisms of destructive chronic inflammation have now been established. Chronic inflammation as the final common denominator for a variety of diseases and conditions provides the reason why anti-inflammatory medications are effective treatments for seemingly diverse skin diseases, cancer, and extrinsic

aging. Recent publications suggest destructive chronic inflammation can be reversed and/or prevented by food, oral supplements, and topical skin care regimens consisting of anti-inflammatory and/or antioxidant ingredients. Thus, physicians treating skin disorders including aging should strongly consider being more focused on reversing and/or preventing inflammation with topical and oral regimes, along with dietary modification. Optimizing the stratum corneum permeability barrier function is also necessary to maximally prevent activation of the destructive chronic inflammation.

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