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CUTANEOUS DETOXIFICATION: THE CENTRAL ROLE OF Nrf2 IN THE SKIN'S ADAPTATION TO ENVIRONMENTAL STRESSES

KEY MESSAGES

* **By regulating the synthesis of antioxidant proteins and detoxification enzymes, the transcription factor Nrf2 represents an essential intrinsic protective mechanism for maintaining skin homeostasis against daily environmental aggressions.**
* **Prolonged or repeated exposure to sunlight and pollution can overwhelm endogenous detoxification capacities, increasing the risk of irreversible cellular damage.**
* **Activating the Nrf2 transcriptional pathway offers a promising target for enhancing the skin's physiological defense mechanisms against sunlght and pollution.**

The skin is constantly exposed to a wide range of environmental stresses. The negative synergy between air pollution and solar radiation represents a particularly harmful combination for skin health[1,2]. Daily exposure triggers a cascade of cellular events **characterized by excessive production of reactive oxygen species (ROS), activation of xenobiotic metabolism**, and induction of inflammatory responses. **These mechanisms accelerate skin aging and significantly increase the risk of carcinogenesis[3].** Fortunately, the skin is equipped with **evolved endogenous defense systems** to counteract these aggressions, with the transcription factor **Nrf2 (Nuclear factor erythroid-2-related factor 2)** playing a pivotal role in regulating **cellular detoxification and antioxidant defenses[3]**. Its activation induces a coordinated response through the production of essential antioxidant and detoxifying enzymes, helping restore skin homeostasis[4]. However, these biological mechanisms can become overwhelmed under chronic or acute exposure to pollutants and solar radiation. Stimulating the Nrf2 pathway emerges as a relevant strategy to potentiate the skin's natural detoxification systems against environmental stresses.

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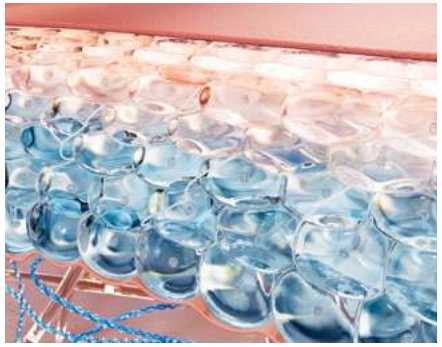
01
ENVIRONMENTAL STRESS EFFECTS ON SKIN

Prolonged and repeated exposure to exogenous factors, such as sunlight (UV rays, infrared light) and atmospheric pollutants, adversely impacts the skin's biological and structural properties. The deleterious effects of solar radiation, including direct DNA damage and increased oxidative stress through ROS production, are well-documented. Meanwhile, due to industrialization, urbanization, and associated climate change, **ambient air pollution has become a major factor in the skin exposome[5,6]**.

The skin is one of the main targets of pollutants, which reach its superficial and deep layers via transcutaneous and systemic routes (particles absorbed by the lungs are transported by the blood to the skin tissue)[5,6].

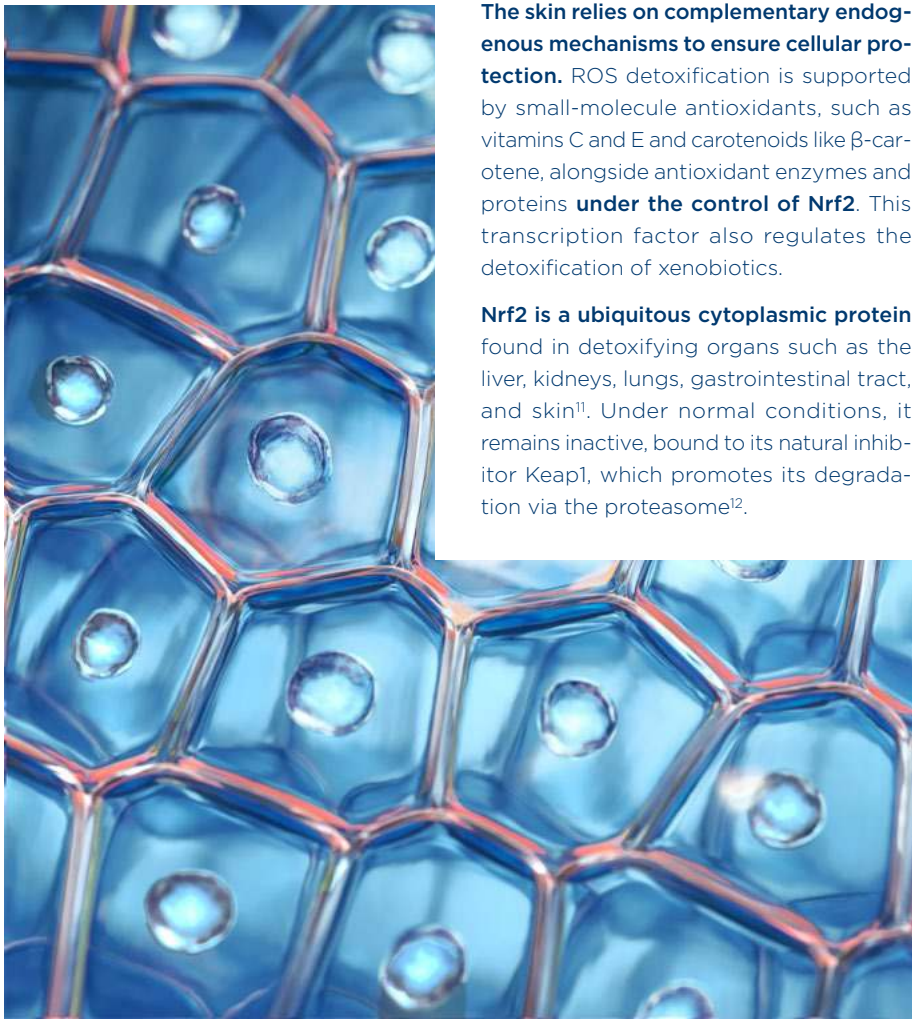


The biochemical and biophysical effects of pollutants on skin metabolism are multifaceted[7]:

- The metabolism of xenobiotics derived from atmospheric pollution can lead to the formation of reactive electrophilic substances, such as quinones. Electrophilic compounds have the ability to form covalent bonds with cellular macromolecules. Their **reactions with DNA** result in the formation of adducts that block replication or induce mutations. Interactions with proteins can cause their irreversible inactivation[8];
- Polluted air also contains pro-oxidant particles, such as polycyclic aromatic hydrocarbons (PAHs), which have the ability to induce **ROS generation** both directly and indirectly[6]. These particles exhibit significant redox activity and stimulate enzymes that produce endogenous ROS. The resulting **oxidation of cellular components**, such as membrane lipid peroxidation[9], impairs their physiological functions. This leads to the accumulation of toxic compounds within cells, potentially causing premature senescence and apoptosis[8]. Simultaneously, ROS-induced cellular alterations activate various signaling pathways that trigger inflammation[10].

02

Nrf2 : A KEY PLAYER IN CELLULAR DETOXIFICATION FOR SKIN HOMEOSTASIS



The skin relies on complementary endogenous mechanisms to ensure cellular protection. ROS detoxification is supported by small-molecule antioxidants, such as vitamins C and E and carotenoids like β-carotene, alongside antioxidant enzymes and proteins **under the control of Nrf2**. This transcription factor also regulates the detoxification of xenobiotics.

Nrf2 is a ubiquitous cytoplasmic protein found in detoxifying organs such as the liver, kidneys, lungs, gastrointestinal tract, and skin[11]. Under normal conditions, it remains inactive, bound to its natural inhibitor Keap1, which promotes its degradation via the proteasome[12].

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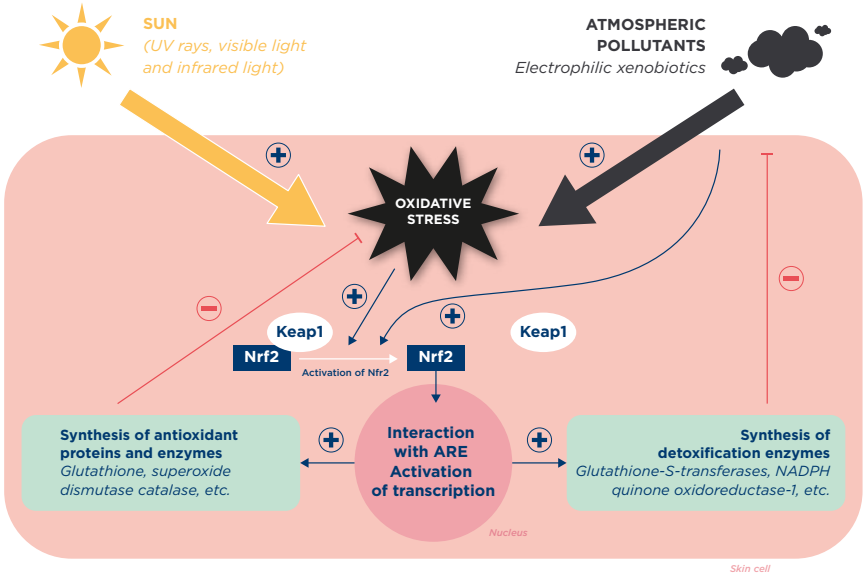

Figure 1: Schematic diagram of Nrf2 activation under physiological conditions. Oxidative stress and electrophilic compounds promote the release of Nrf2 from its natural inhibitor, Keap1. After translocation into the nucleus, Nrf2 interacts with the ARE-specific DNA sequence to activate the transcription of genes encoding detoxification and antioxidant enzymes, thereby maintaining cellular homeostasis.

In the presence of electrophilic xenobiotics or redox imbalance, Nrf2 is released from Keap1, migrates to the nucleus, and binds to the Antioxidant Responsive Element (ARE) on DNA. This process activates the transcription of over 200 genes critical for skin homeostasis[13,14] (Figure 1):

- **Antioxidant activity:** Nrf2 regulates intracellular antioxidant responses by inducing the **synthesis of universal endogenous antioxidants** such as glutathione, superoxide dismutase, and catalase to neutralize ROS[15];
- **Detoxifying action:** Nrf2 stimulates the **production of detoxifying enzymes**, such as glutathione-S-transferase and glutathione peroxidase, which conjugate xenobiotics into water-soluble molecules for cellular elimination[15,16]. Metallothionein 1G sequesters toxic heavy metals, reducing their interactions with sensitive cellular components[17].

Several *in vitro* and *in vivo* studies highlight the essential function of Nrf2 in protecting the skin against sunlight and pollution, particularly in preventing cutaneous carcinogenesis[18,19]. For instance, studies by auf dem Keller *et al.* report increased incidence and multiplicity of skin tumors in Nrf2-deficient mice following topical application of carcinogens[20]. This response correlates with reduced expression of Nrf2-regulated detoxifying enzymes, such as NAD(P)H quinone oxidoreductase 1 (NQO1)[20].

03
TARGETING Nrf2 TO STRENGTHEN THE SKIN'S DEFENSE MECHANISMS

Although the skin has innate detoxification systems, **excessive and daily exposure to sunlight and pollution can dysregulate the Nrf2-Keap1 pathway, limiting its ability to neutralize ROS and xenobiotics and maintain homeostasis**. High UV doses have been shown to reduce Nrf2 activity, decreasing antioxidant enzyme expression and amplifying skin damage[18]. Similarly, Nrf2 expression diminishes in UV-exposed fibroblasts[20]. In addition, **Nrf2 expression declines with aging**, rendering the skin more vulnerable to environmental aggressors[22,23].

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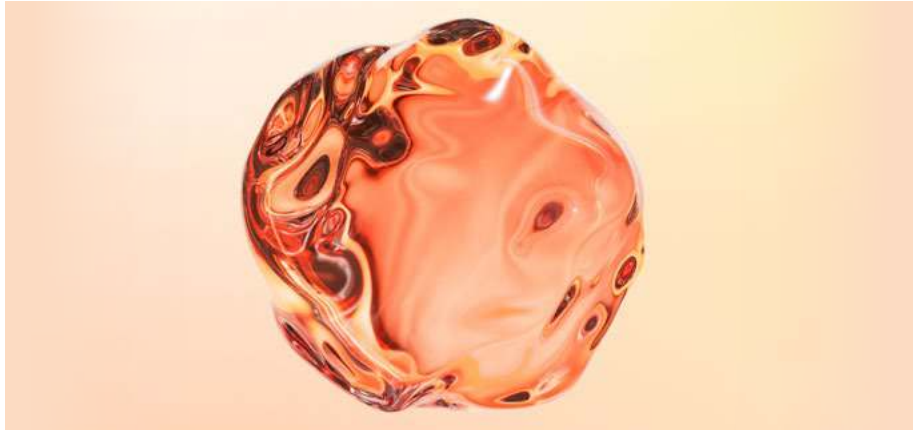
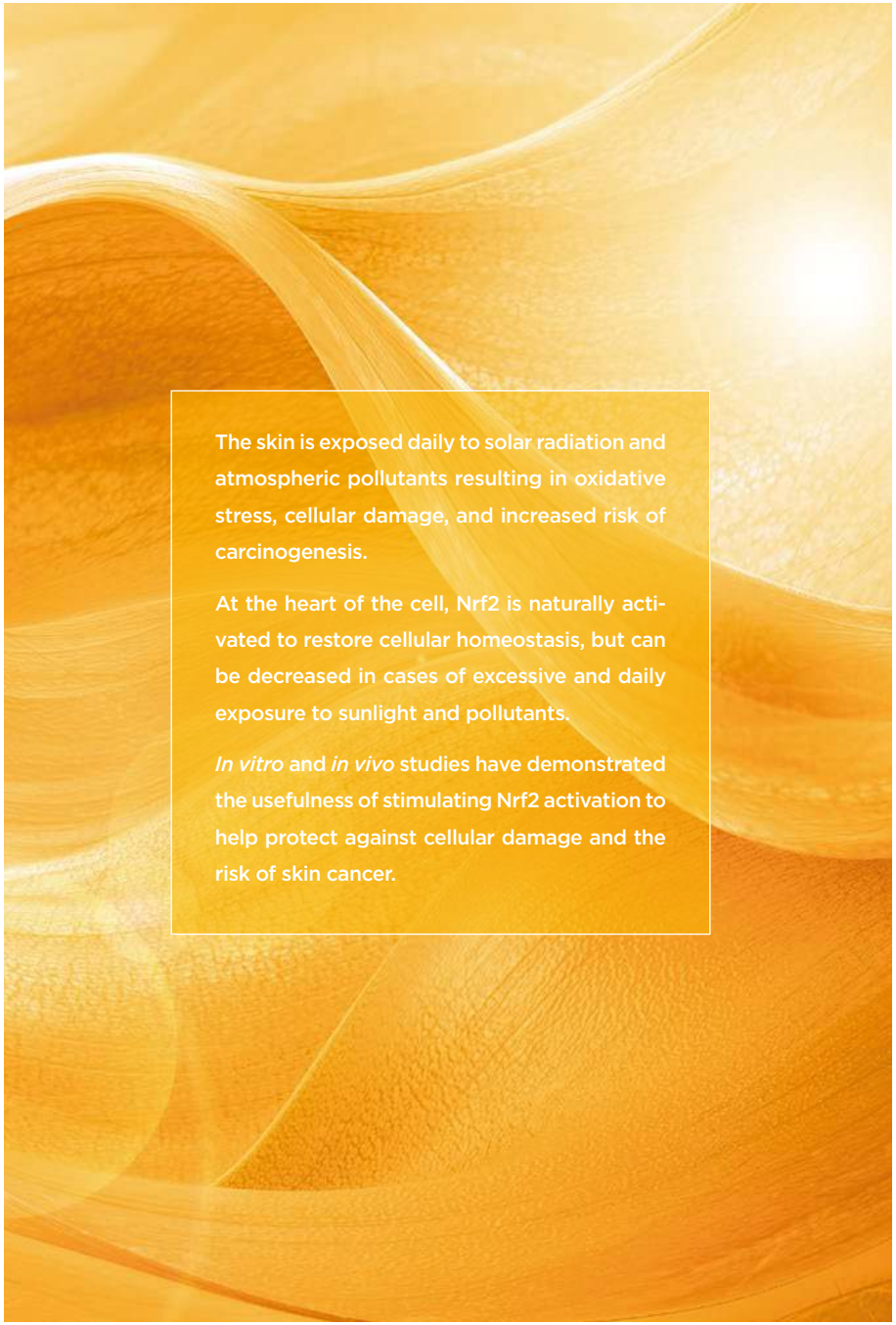


Given increasing exposure to atmospheric pollution and solar radiation, activating Nrf2 directly or indirectly offers a complementary strategy to strengthen natural detoxification pathways, limit skin damage, and reduce carcinogenesis risks. Several Nrf2 activators have demonstrated efficacy against photoaging and photocarcinogenesis:

- ***In vitro*:** in human keratinocytes, Nrf2 activation reduces UV-induced ROS production, decreases lipid peroxidation, and enhances antioxidant enzyme activity[21,24].
- ***In vivo*:** topical application of a Nrf2 activator in mice reduces UV- and visible light-induced oxidation by maintaining intradermal carotenoid levels[24]. Similarly, a Nrf2 activator applied to the skin of mice predisposed to cutaneous squamous cell carcinoma through chronic UV exposure decreased tumor incidence, multiplicity, and volume by approximately 50%, correlating with the induction of cytoprotective responses in the skin[26].
- **Clinical evidence:** in a randomized, double-blind, controlled trial, topical Nrf2 activation in healthy subjects reduced simulated UV-induced erythema, a marker of skin damage and skin cancer risk[27].



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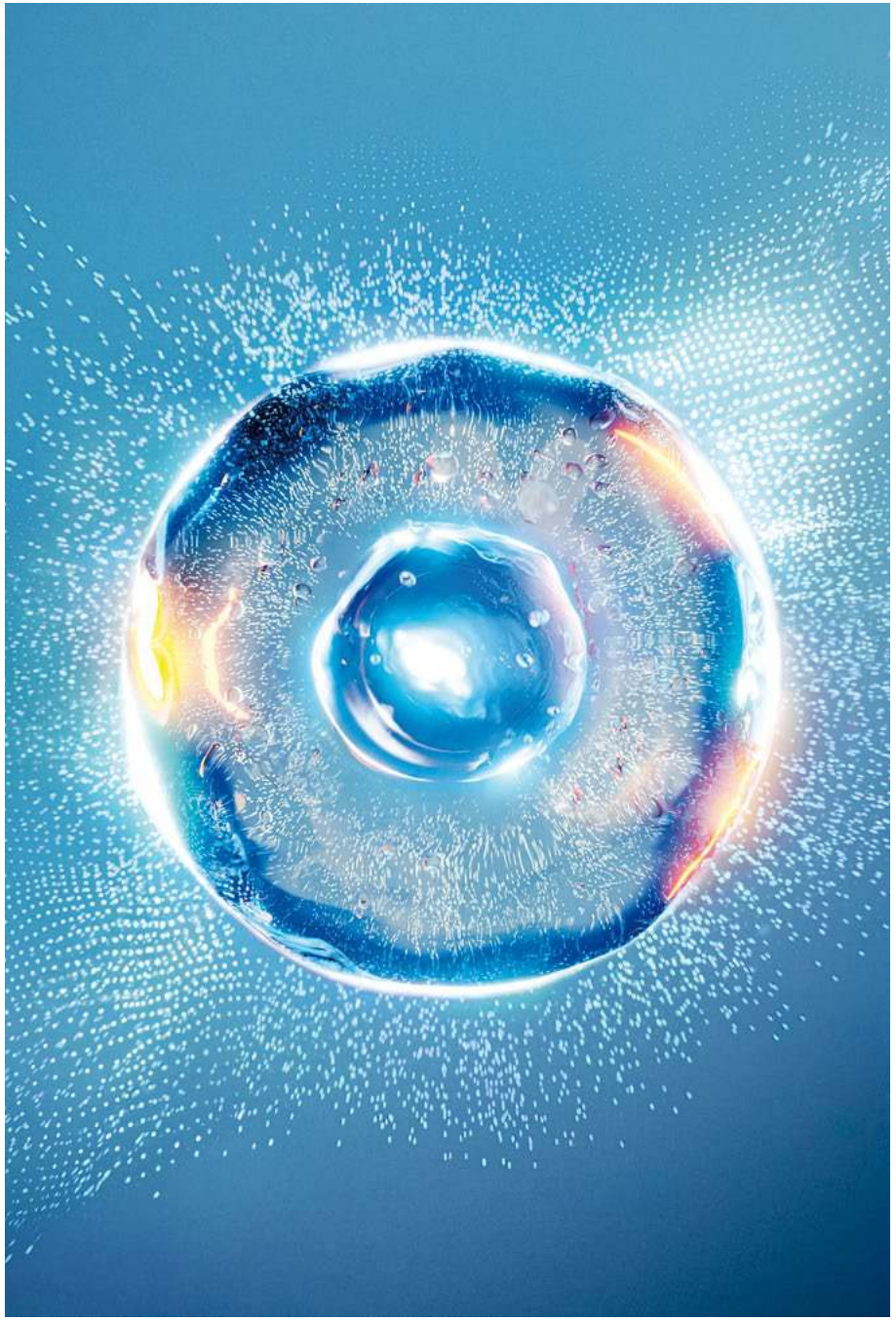

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