# Mechanisms of Skin Aging Processes

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With the advancement of living standards in modern society and the emergence of an aging population, an increasing number of people are becoming interested in the topic of aging and anti-aging. An important feature of aging is skin aging, and women are particularly concerned about skin aging. In the field of cosmetics, the market share of anti-aging products is increasing year by year.

anti-aging ingredients | inflammation | photoaging | reactive oxygen species | skin aging

## 1. Introduction

Currently, the global population will continue to experience aging, with some developed and developing countries in particular moving towards severe aging populations in their societies. South Korea and Japan will become the two countries with the most severe aging populations [1]. Some experts point out that China will exhibit a moderately-aging society in 2023. According to a report, in 2022, the population aged 60 and above will have reached 28.04 million, accounting for 19.8%; among them, the population aged 65 and above was 209.78 million, accounting for 14.9% [2]. As the population is becoming an aging society and the living standards are improving, there is now a growing interest in the topic of aging among modern societies as they seek to understand and counter the adverse effects of aging. One of the most prominent features of aging is skin aging, which is of particular concern to women. According to the statistics, the proportion of Chinese women taking anti-aging measures is 90%, and the size of China's anti-aging market reached CNY 64.6 billion in 2020 [3].

The main characteristics of skin aging are skin relaxation and wrinkles [4], which are related to skin cell aging and decreased collagen synthesis or increased degradation [5][6]. The causes of skin aging can be divided into endogenous and exogenous factors [7]. Endogenous factors mainly involve the accumulation of time and the influence of related physiological traits, while exogenous factors mainly include ultraviolet radiation, smoking, wind exposure, and exposure to harmful chemicals [8][9]. These incentives, especially exogenous ones, will cause macromolecular structural damage and related functional changes in skin cells, thus leading to accelerated skin aging [10]; however, the mechanisms of skin aging and effective compounds or products against skin aging are not well understood.

New compounds or drugs to be used against skin aging are increasingly added into books and onto shelves. The current compounds or drugs used against skin aging can be orally administrated or locally applied onto the skin according to their characteristics of pharmacokinetics; however, for oral administration, a low bioavailability could occur and it may be difficult for those compounds to reach the skin tissues. For local application on the skin, these

compounds or drugs still have limitations in their chemical stability and a lack of transdermal absorption, limiting their application in the cosmetics field. These compounds or drugs, therefore, should be further improved in pharmaceutical preparations, and a new drug delivery system may enable these chemicals to have a better absorption and better skin anti-aging activity [11].

## 2. Classic Theories on the Mechanism of Skin Aging

At present, classic theories on the mechanism of skin aging include the theory of free radicals and oxidative stress, the theory of inflammatory aging, the theory of skin photoaging, and the theory of nonenzymatic glycosyl chemistry. These main theories are briefly described below.

- Free radicals and oxidative stress theory

Free radicals are one of the main causes of decreased body function and skin aging. Reactive oxygen species (ROS) are a type of unstable molecule that contain oxygen and that easily react with other molecules in a cell. Oxidative stress refers to the imbalance between intracellular oxidation and antioxidant activity, where cells tend to oxidize and produce a large amount of ROS. During cell metabolism, mitochondria produce ROS through oxidative metabolism. When there is too much ROS in cells, the mitochondria will be damaged, the production of mitochondrial ATP will be reduced, the mitochondrial membrane potential will be reduced, and a chain reaction will be generated to accelerate aging [12]. Excessive ROS can also damage the DNA structure, causing aging symptoms such as cell function damage and cell replication disorders [13][14]. A significant increase in the ROS levels not only accelerates skin replication aging, but also promotes a decrease in the collagen levels in skin tissue, leading to skin relaxation and wrinkles [5]. The molecular mechanism is related to the increase in matrix metallopeptidase (MMP) expression [15][16][17][18]. MMP is a kind of zinc-dependent endogenous protease. MMP can specifically degrade the extracellular matrix, including collagen, and can cause damage to the extracellular matrix, which ultimately leads to skin aging. Consequently, removing excess ROS from the skin cells has become one of the most common ways to combat skin aging [15].

- Inflammation theory

Inflammation is one of the major causes of cellular senescence. “Inflammatory aging” is characterized by increased levels in the proinflammatory factors in the body. These changes will lead to the aging of body cells, including the skin, and induce many aging diseases [19][20]. At the skin level, senescent fibroblasts and keratinocytes secrete a large number of “senescence associated secretory phenotypes (SASP)”, including the proinflammatory cytokine TNF-α, IL-1, IL-6, IFN-γ and MMPs and others [21]. These pro-inflammatory cytokines induce skin cell senescence by promoting the production of ROS and activating the ATM (ataxia telangiectasia mutated)/p53/p21-signaling pathway. At the same time, when skin cells develop inflammation, this will lead to an increased release of MMPs, which will cause the degradation of collagen, resulting in the relaxation of and wrinkles in the skin cells [22][23]. Inhibiting skin cell inflammation is, therefore, one of the important strategies to control skin cell aging.

- Photoaging theory

External factors such as ultraviolet (UV) light in sunlight play a very important role in the process of skin aging. UV plays a diverse role in the anti-aging of skin, with different wavelengths having diverse effects and systemic implications. The specific wavelength of UVR determines the nature of the signals it transduces, affecting the local neuroendocrine axes, and may induce skin aging [24]. According to the mechanism theory of photoaging, ultraviolet light can lead to the production of ROS and the secretion of MMPs [25]. Long term exposure to solar ultraviolet radiation will cause photoaging, which will affect pigmentation, immunity and the vascular system [26][27]. Adult dermal collagen content decreases every year, and the decrease in collagen is mainly caused by the increase in MMP expression and the decrease in collagen synthesis [28]. With an increase in age, the levels of MMP-1, 2, 9 and 12 increase, while the expression of procollagen mRNA decreases significantly, which leads to a decrease in dermal collagen content. Significant evidence has proved that MMP plays a major role in inducing the onset of photoaging. UV irradiation induces keratinocytes and fibroblasts to secrete MMPs, which in turn degrade the dermal extracellular matrix components such as collagen [29]. Inhibiting skin UV irradiation and its related damage is one of the important strategies to prevent skin cell aging.

- Nonenzymatic glycosyl chemistry theory

Internal factors such as nonenzymatic glycosylation (known as a Maillard reaction) also play a very important role in skin cell aging. According to this theory, the crosslinking damage of proteins caused by glycosylation is the main reason for aging [30]. This glycosylation is a nonenzymatic reaction between free reducing sugars and free amino groups of proteins, DNA and lipids, resulting in advanced glycation end products (AGEs) [31]. The accumulation of AGEs will affect cellular homeostasis and protein structure changes, leading to skin darkening and aging. The accumulation of AGEs also leads to ROS production and inflammation, thus accelerating skin aging, and the formation of AGEs is irreversible. Moreover, skin cells age at high levels of glycation [32][33][34]. With an aging of the population, the number of diabetic patients will increase significantly, and skin glycosylation will be more common [35]. Inhibiting skin glycosylation is also one of the important ways to control skin aging.

In addition to the four theories mentioned in this research, genetical factors, DNA repair and stability, cellular senescence and telomeres, mitochondria, apoptosis, estrogen deficiency, circadian rhythms, neuroendocrine, diseases, physical activity, stress, and other environmental factors (e.g., diet, pollution and smoking) are also important in the field of skin aging, and have been studied in animal and experimental studies on cell cultures [36][37][38][39][40]. Additionally, skin as a stress sensor, modulates homeostasis via the neuroendocrine and immune systems, and signaling molecules. It protects against stressors through keratinocyte differentiation, the pigmentary system, and communication with the dermis/hypodermis. Dysfunctions can cause various skin disorders and aging [41].

Based on the descriptions above, the mechanisms of skin aging are mainly related to an increase in the intracellular ROS level and oxidative stress, an increase in the inflammatory level, and a subsequent decrease in the collagen level. Excessive external UV irradiation and an enhanced internal microenvironment such as glycation

are also important factors that lead to skin aging, but the basic mechanism is still related to the upregulation of skin cell ROS and an increase in oxidative stress and inflammation. It is, therefore, very critical to inhibit the production of skin cell ROS in order to attenuate the aging of the skin. In addition, the direct upregulation of collagen level is also one of the important strategies to repair skin cells and reduce skin wrinkles.

A summary of the mechanism of the skin aging processes is shown in **Figure 1**.

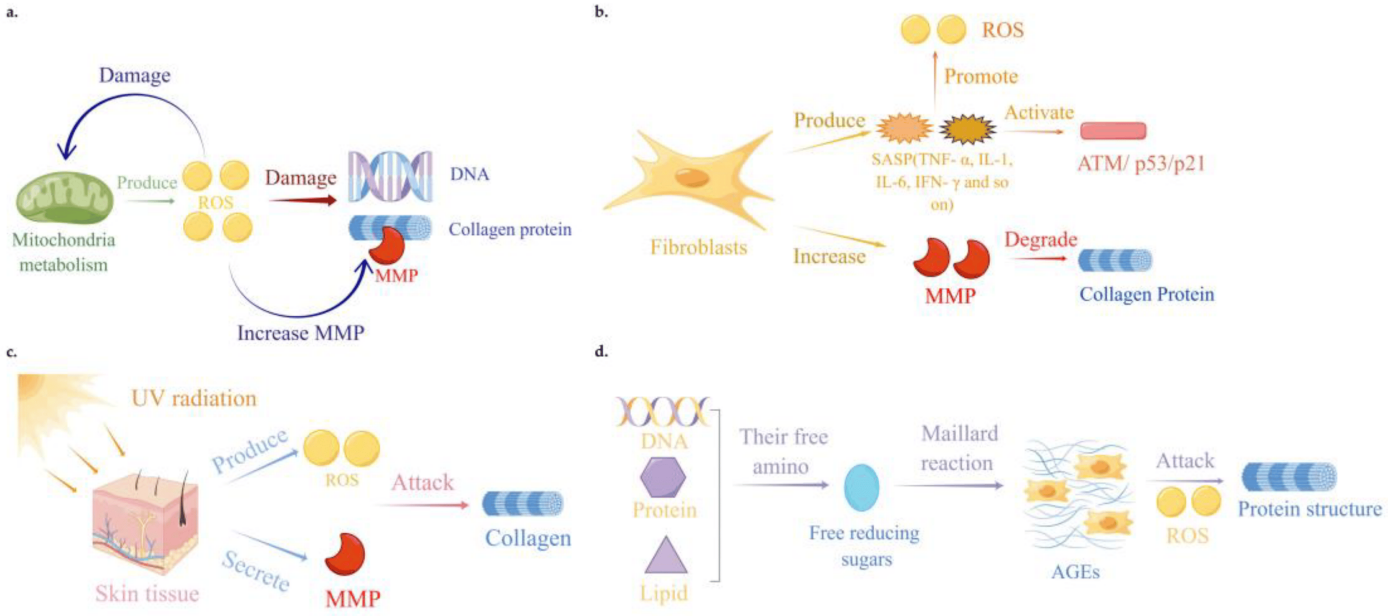


**Figure 1.** Mechanisms of skin aging processes. (**a**) Free radicals and oxidative stress theory. Mitochondria produce ROS through oxidative metabolism. Excessive ROS can damage the mitochondrial and DNA structures, leading to a decrease in collagen levels and an increase in MMP levels in skin tissue. (**b**) Inflammation theory. Senescent fibroblasts and keratinocytes secrete a large number of senescence-associated secretory phenotypes, including TNF-α, IL-1, IL-6, IFN-γ and MMPs. These proinflammatory cytokines induce skin cell senescence by promoting ROS production and activating the ATM/ p53/p21-signaling pathway. (**c**) Photoaging theory. Ultraviolet irradiation induces the production of ROS and the secretion of MMPs, which degrades skin extracellular matrix components such as collagen. (**d**) Nonenzymatic glycosyl chemistry theory. Non-enzymatic glycosylation is a reaction between free reducing sugars and free amino groups of proteins, DNA and lipids to produce AGEs and ROS. The accumulation of AGEs, together with ROS, can lead to changes in the cell homeostasis and protein structure. These images were drawn with the Figdraw software1.0.

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