

Role of microRNAs in skin aging and its potential therapeutic interventions

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Abstract

The skin, the largest and most important organ of the body, serves diverse functions such as protection from the outside, temperature regulation, *etc.* It is composed of 3 layers: hypodermis, dermis, and epidermis. As the skin ages, it undergoes morphological and anatomical changes. Wrinkle formation and sagging are the main physical changes visible on the skin. Aging is caused by extrinsic and intrinsic factors that affect the morphology and function of the skin. Intrinsic aging is driven by biological and genetic factors, while extrinsic aging is influenced by environmental factors. Recent findings show the contribution of miRNAs in skin aging, particularly in replicative senescence. They regulate the expression of genes post-transcriptionally and control functions like collagen modulation, elastin synthesis, *etc.* This review explores the role of miRNAs in skin aging and details their role in cellular functions, including collagen synthesis. This review also describes the types and characteristics of skin aging, structural alteration in different layers of skin, and therapeutic interventions of miRNA in skin aging. Knowledge of miRNA involvement in aging will help to introduce new therapies in anti-aging and skin care technology. The intricate relationship between environmental and genetic factors that cause skin aging is discussed, emphasizing the role that miRNAs play in this complex process. In addition, potential therapeutic interventions are described, highlighting the need for deeper knowledge of the molecular mechanisms of skin aging for effective, innovative future research.

Keywords: Skin aging, miRNA, collagen, cellular senescence, therapeutic interventions, skin structure

Introduction

As the largest and most diverse organ in the body, the skin performs a variety of functions, including regulating body temperature, shielding the body from external agents and infections, and resisting moisture. The entire skin layer serves as a barrier to protect the body from the elements

[1]. It consists of 3 distinct layers: the hypodermis, dermis, and epidermis. The epidermis is primarily composed of keratinocytes. It is also composed of melanocytes and Merkel cells. The second layer, the dermis, helps with blood and nutrient circulation. It consists of blood vessels, connective tissue, nerves, *etc.* The hypodermis, the bottom layer of the skin, stores energy and connects the skin to bones and muscles. It is composed of connective tissue and adipose tissue [1, 2]. Aging is an inevitable phenomenon that leads to a gradual loss of tissue integrity. [Figure 1](#) shows the structure of normal and aged skin.

The most apparent manifestation of this skin aging is characterized by various changes, including the development of wrinkles, sagging, and pigmented spots [3]. The skin is the most visible organ in the body and all alterations, including aging, are easily observed. Aging is a broader concept encompassing overall alterations in the appearance of skin and dermal tissues, along with their functions.

It is interesting to note that cellular senescence is a concept that describes the condition in which individual cells

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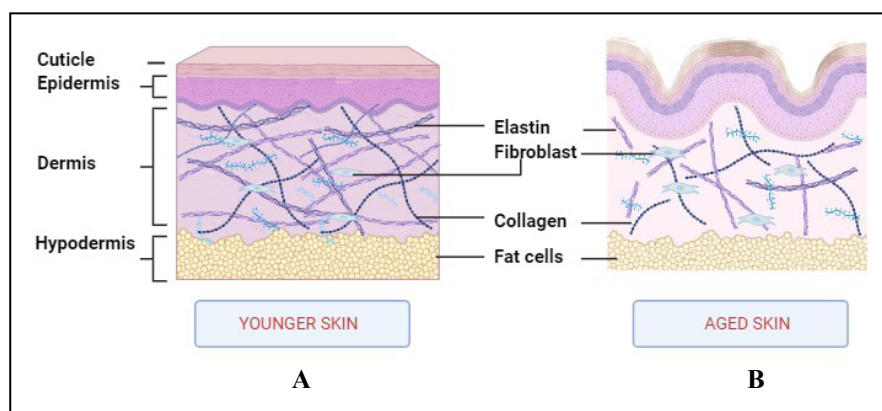


Figure 1. The structure of aged skin in comparison to normal young skin. (A) Normal skin contains elastin, collagen, fibroblasts, and fat cells in different skin layers in a connected manner. (B) Aged skin with disrupted elastin, collagen, fibroblasts, and fat cells in skin layers. During aging, the synthesis of collagen and elastin decreases and their network breaks down, leading to wrinkling and sagging of the skin.

experience permanent growth arrest. Hayflick and Moorhead were the first to define aging at the cellular level by demonstrating the limited ability of human primary fibroblasts to divide. The replication process causes telomeres to become unable to maintain their length, which results in the so-called Hayflick limit. As a result, cells lose their ability to proliferate and enter an irreversible cell cycle arrest known as cellular senescence [2, 4]. Cellular senescence is one of several factors that lead to skin aging.

Skin aging is a more complex phenomenon involving both morphological and functional changes in the skin over time. Moreover, the aging phenomenon affects the skin in various ways, including thinning of the epidermis and a remarkable decrease in the turnover rate. The integrity of the skin and its physiological features are also affected. Although men and women age differently, the appearance of their skin also varies, but the internal and external factors are the same [5, 6]. This natural progression involves a complex interaction between intrinsic and extrinsic factors, which is why it is classified as intrinsic and extrinsic aging [4, 6]. Genetic and biological components are considered intrinsic or internal variables, whereas environmental exposures and lifestyle choices are extrinsic or external factors. The effects of intrinsic aging on the skin are similar to those on other internal organs. It is also known as chronological aging because time is another factor that causes it. In addition, the two main signs of natural aging are the flattening of cells at the epidermal-dermal junction and the thinning of the dermis, which is a layer of skin. Moreover, elastin and collagen in the skin break down over time, reducing the integrity and stability of the skin [7]. In contrast, extrinsic aging, also known as photoaging, is induced by sun exposure and manifests itself in exposed areas of the skin, such as the backs of the arms and the face [8]. It is characterized by visible signs such as dark spots, wrinkles, and a rough, leathery skin texture. Additionally, reduced elasticity, abnormal coloration, graying hair, and hair loss are other results of photoaging [9].

Although skin aging is a normal aspect of life, the external indicators of aging can have a major impact on how someone feels about themselves. Therefore, it is essential to understand the cosmetic elements. In addition to these cosmetic consequences, skin aging also has functional consequences. With age, changes in the skin's structure can compromise its protective functions. To detect ab-

normal growth and maintain homeostasis, the skin relies on molecular signals due to its diverse functions and cell types [10]. These pathways contribute to morphological and functional changes in the skin. However, a common hallmark of aging is the up- and downregulation of protein expression associated with the electron transport chain. Whether this is a cause or a consequence of aging remains controversial [11]. To understand the genetic aspects of aging, several studies have been conducted on protein and gene expression in various aging model systems. An emerging focus in these investigations is on small non-coding RNAs, particularly microRNAs, which act as potent post-transcriptional regulators [12]. Over the past decade, research on miRNAs has revealed their role in all cellular processes. These small regulatory molecules play an integral role in fundamental cellular activities such as cell proliferation, differentiation, aging, *etc.* [13]. They also play a crucial role as biomarkers in various diseases. MicroRNAs (miRNAs) are non-coding RNAs found in all organisms and plants. They are approximately 25 nucleotides in length. These molecules are involved in the post-transcriptional regulation of gene expression by binding to their target [14]. Recently, miRNAs have been discovered to be significant regulators of aging and senescence. These short RNAs play an important role in modulating the expression of mRNA targets, leading to translational repression or degradation of mRNA. This promotes protein degradation or prevents translation [7]. There are several miRNAs that are commonly involved in many skin activities, including collagen modulation, keratinocyte differentiation, *etc.* Altered expression of miRNAs prevents proliferation of cells, affects elastin production, imbalances skin cell turnover, increases oxidative stress, *etc.* [2, 10]. Moreover, miRNAs have become common regulators of a number of skin disorders and may serve as new biomarkers or therapeutic targets for etiology or treatment. In short, miRNAs have a variety of functions in skin biology and their intricate roles make them more potential candidates for further studies and research in the field of dermatology and skin therapy [2]. In the present review, our objective is to focus on the contribution of miRNAs in skin aging. The primary objective of this review is to deliver extensive knowledge in the field of skin aging and the role of miRNAs in the aging process. This understand-

ing of miRNA involvement in aging provides the basis for developing innovative therapies and pioneering in a new era of anti-aging interventions and skin care technology.

Skin structure

The skin is the largest part of the body that provides protection from the external environment. It accounts for 8 to 15% of total adult human body weight and occupies 1.8 m² of surface area [11, 15]. It is also a complex and dynamic organ with multiple functions. In addition, the skin maintains the homeostasis of the body by preventing the loss of electrolytes, proteins, and fluids, along with temperature regulation [1, 16]. The epidermis, dermis, and hypodermis are three distinct layers that make up the skin and are functionally connected layers [17]. The structure of the skin is illustrated in Figure 2.

The outermost layer of the skin, derived from the ectoderm, is called the epidermis. It protects the body from the external environment, including ultraviolet (UV) protection, thermoregulation, and immune protection. Keratinocytes, melanocytes, inflammatory cells, Langerhans cells and neuroendocrine cells are the main cell types of the epidermis. Among these, keratinocytes cover most of the epidermis, and they're interconnected by tight junctions [11].

They produce keratin, which contributes to the skin's waterproofing properties. Melanocytes synthesize the pigment melanin, which provides color and UV protection [17, 18]. The epidermis is arranged in several layers, including the stratum spinosum, stratum basale, stratum granulosum, and stratum corneum (Figure 2A). The outer layer of the epidermis is called the stratum corneum, which consists of flattened keratinocytes that provide protection from external factors. The stratum basale is the innermost layer of the epidermis, where new cells are formed. As they move toward the surface, the cells

eventually become flattened [4]. In a recent study, keratin fibers stiffened in naturally aged skin and water movement in the stratum corneum also decreased [19, 20]. The number of melanocytes and Langerhans cells decreased, leading to epidermal thinning [19].

Beneath the epidermis is the dermis. The dermis is mainly involved in nutrient supply to the cells of the skin. It is a connective tissue layer composed of collagen and elastin fibers that are interconnected. This layer is rich in lymph, nerves, hair follicles, and sweat glands [2, 11]. It is also populated with lymphocytes, macrophages, dendritic cells, *etc.* Apart from nutrient supply, it also provides oxygen and detects touch and pain [1]. Dermis cells are mostly presented by fibroblasts and are predominantly involved in extracellular matrix (ECM) components. The ECM is composed of collagen and glycosaminoglycan embedded with mast cells, neural cells, and endothelial cells [21]. The dermis is divided into two layers: the reticular and papillary dermis (Figure 2B), which work together to perform all functions. The papillary dermis connects the epidermis and blood vessels, while the reticular dermis provides strength to the skin [22]. The density and thickness of dermal collagen decreases in chronologically aged skin. Although photoaging leads to a decrease in the number and size of blood vessels, it can induce angiogenesis [19, 23].

The hypodermis, called the subcutaneous layer, is located just below the dermis and consists of loose areolar connective tissue with abundant adipose tissue and less collagen content. It is the deepest layer of the skin (Figure 2C). This layer enables cutaneous mobility. Metabolic energy is stored in the adipose tissue of the hypodermis and it also provides thermal insulation [24]. This layer contributes to the insulation of the body and offers a protective cushion for internal organs. Vitamin D is also produced in this layer [1]. The hypodermis of aged skin exhibits reduced ability to both maintain protective barriers and recover from damage [4, 25]. Aging also leads to decreased cell proliferation in the basal layer, causing the hypodermis to

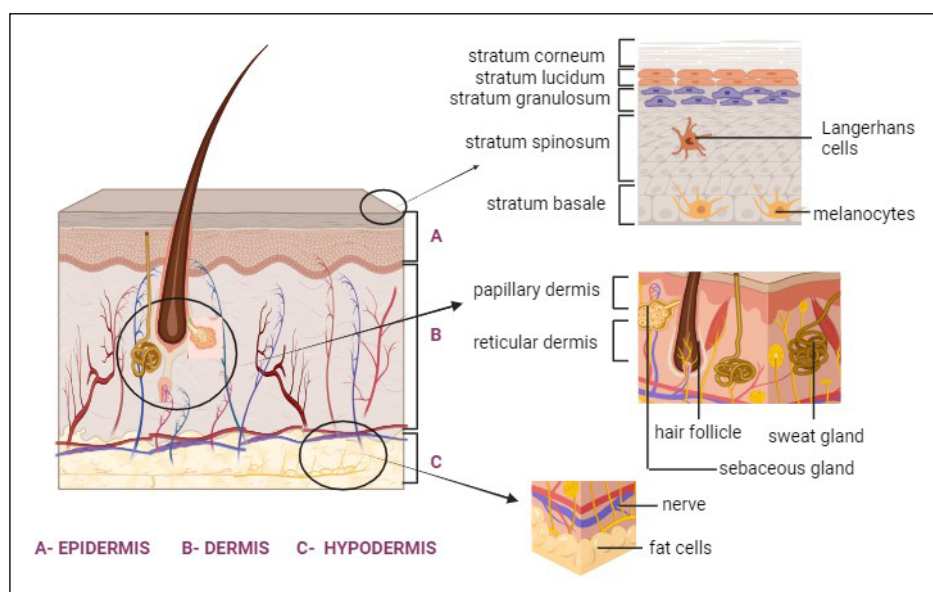


Figure 2. The structure of the skin. (A) EPIDERMIS is the outer layer of skin that comprises the Stratum corneum, Stratum lucidum, Stratum granulosum, Stratum spinosum, and Stratum basale. (B) DERMIS is the second layer below the epidermis. It consists of the Papillary dermis and the Reticular dermis. This layer is characterized by hair follicles, sweat glands, and sebaceous glands. (C) HYPODERMIS, which is the deepest layer, contains nerve and fat cells.

thin and reducing contact between the dermis and epidermis. Consequently, this reduces the nutrient supply to the epidermis and weakens the renewal capacity of cells [4]. Approximately 30,000 dermal cells perish every minute, emphasizing the continuous renewal processes inherent to the skin. Successful skin development and regular physiological functions hinge on the coordinated interplay of genetic networks and regulatory factors [26]. The skin maintains a constant self-renewal mechanism to replenish injured or old cells in spite of constant exposure to environmental pollutions and facilitate tissue repair. However, when its regenerative ability decreases with age, it can trigger cellular senescence, paving the way for the onset of various dermatologic conditions [27].

Skin aging—types and characteristics

The appearance and functionality of the skin will gradually change due to numerous biological and physiological processes leading to aging [28]. Skin wrinkling, dry skin, skin thinning and sagging are the main characteristics [3]. In addition, it causes age spots, hyperpigmentation, decreased elasticity, and other issues. The skin, which serves as the body's barrier, is constantly exposed to a variety of external and internal stimuli, which causes a progressive loss of regenerative potential [4]. Along with structural and functional alterations in extracellular matrix skin components such as collagen, elastin, and others, aging processes also bring about phenotypic changes in cutaneous cells [29]. Skin aging occurs in two forms: intrinsic and extrinsic. Natural aging, another term for intrinsic aging, is mainly caused by genetic factors, whereas extrinsic aging is influenced by environmental factors such as sunlight [9, 13]. Apart from that, apoptosis, DNA damage and telomere shortening are some of the aspects that cause skin aging.

Intrinsic aging is the term for a natural physiological process that causes wrinkling in dry skin [9, 30]. Histologically, a flat epidermal-dermal interface and the absence of dermal papillae are characteristics of skin that is intrinsically aged. However, normal epidermal differentiation and cellular polarity appear to be preserved [13, 31]. Collagen synthesis is reduced, as is the ability to heal wounds. Moreover, atrophy of the dermis may occur due to a reduced repair capability, which will not be able to restore collagen fibers that have been degraded by this process [8, 32]. The number of blood vessels is also decreased which causes a decreased blood supply to cells. Apart from genetic factors, other elements that drive intrinsic aging are hormones and time. It is an interesting fact that the telomere, the terminal region of the eukaryotic chromosome, significantly influences intrinsic aging. Telomeres contain a short sequence of nucleotides, TTAGGG. Repeated cycles of replication ultimately lead to the loss of protection at the end of the chromosome (particularly this sequence), making it susceptible to end-to-end fusions. This condition is incompatible with regular cell functioning. Most cells can divide up to 60 or 70 times over their lifetimes before

entering senescence, a state in which they are still viable but unable to divide [32]. Oxidative stress also contributes to skin aging, eventually causing the accumulation of oxidative damage to proteins, lipids, and other constituents of cells. It's connected to a gradual reduction in antioxidant capability and an increase in the formation of reactive oxygen species (ROS). Inflammation, which causes ROS production as well as activation of pro-inflammatory cytokines [33]. Another element contributing to skin aging over time is a modification in the levels of growth factors and apoptosis. Moreover, hormones like melatonin have been observed to decrease as well. At the same time, signaling molecules also play a vital role in aging. Particularly, certain signaling molecules became more abundant with age, whereas others, such as chemokines, declined and caused the destruction of various skin functions [34, 35]. Histological alteration observed in the skin includes changed stratum corneum permeability, decreased water loss that is attributed to a hardened and thickened stratum corneum, and changed lipid composition causes greater cellular cohesion. In addition, the number of fibroblasts and mast cells in the dermis also decreased [19].

Extrinsic aging is mainly affected by skin exposure to environmental factors such as sunlight and pollution. Lifestyle also contributes to photoaging. These substances degrade the collagen and elastin fibers of the skin [29]. Paul Gerson Unna observed in their study that there was a transformation in the skin of sailors, particularly in areas exposed to the sun, leading to premature aging. Studies have shown that UV radiation is the key element in extensive aging, which accounts for 80% of facial aging [36]. The process of UV-induced skin aging is complex and can be initiated by multiple signaling pathways, such as telomere DNA destruction, protein oxidation, mitochondrial damage, and other signaling initiated by receptors [37]. In addition, in the late 19th century, Harry Daniell found that smokers appeared older than non-smokers. Thus, alcohol and smoke also contribute to extrinsic aging [38-40]. The histological signature of photoaging is characterized by dermal elastosis, marked by the presence of thickened, intertwined, and finally granular elastic structures. In contrast to intrinsic aging, photoaged skin forms thick layers with irregular pigmentation, large wrinkles, and elastosis [41]. Compared to chronologically aged skin, photoaged skin has a thicker epidermal layer. Furthermore, UV exposure may increase the number of keratinocytes and melanocytes [19, 42]. The prevalence of pathologically altered elastic fibers, sometimes referred to as "solar elastosis", is the most prominent histological characteristic of photoaging. The activation of matrix metalloproteinases (MMPs) is the main cause of the destruction of elastin and collagen structures. Furthermore, lymphocytes, mast cells, eosinophils, and other inflammatory cells are elevated in extrinsic aging [19]. However, all skin layers are affected by aging and show changes in their roles and morphology [43].

Pathways involved in aging

Aging consists of several interconnected processes that are driven by genetic programming, continuous external inputs, and internal metabolic reactions. All organs and systems are impacted by aging, although at different rates [11, 44]. With aging, the morphological and physiological functions of the skin, like all other organs, gradually deteriorate. As a result of the progressive diminishing of cellular constituents, mechanical protection is weakened. This slows down the immune response, which leads to an imbalance in thermoregulation [45]. Increased levels of matrix metalloproteinases (MMPs) and matrix-degrading enzymes, released primarily by epidermal keratinocytes and dermal fibroblasts, cause a decrease in extracellular matrix (ECM) formation in the dermis, which results in the morphologic manifestation [46]. These MMPs are involved in the degradation of collagen fibers, a characteristic feature of intrinsic aging, and the partial degradation of elastin fibers, a process associated with extrinsic aging. Imbalances in oxidative stress and inflammatory processes further intensify the activity of MMPs, which will also contribute to skin aging [30].

Although the two types of aging are distinct, it appears that identical molecular pathways underlie both forms of skin aging. In fact, the breakdown of the extracellular matrix by upregulated MMPs and the production of ROS are shared characteristics of skin aging in both types. ROS are free oxygen radicals and other oxygen-derived molecules that are highly reactive. With aging, ROS accumulate and lead to the inactivation of protein tyrosine phosphatases (PTPs or RPTPs), thereby activating receptor tyrosine kinases (RTKs). These RTKs can also be activated by other factors such as inflammatory cytokines and growth factors. Moreover, RTK activation is not uniformly increased in aged skin; some RTKs may decrease with aging. Activated RTKs undergo phosphorylation, triggering downstream signaling pathways. This phosphorylation cascade activates three families of mitogen-activated protein kinases (MAPK), such as extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK) and p38MAPK. Subsequently, the transcription factor AP-1

(activator protein-1) is activated downstream of these MAPK pathways. This activation leads to the expression of various MMPs, including MMP-1, MMP-3, and MMP-9, while simultaneously inhibiting the expression of procollagen-1. Basically, ROS-induced signaling prompts a cascade of molecular reactions that activate pathways involved in the breakdown of the ECM and inhibit procollagen-1 expression. Inhibition of procollagen-1 expression disrupts the regular synthesis of collagen, which causes the loss of structural and functional integrity of dermal tissues. Ultimately, it causes problems related to elasticity and thus aging [19, 47, 48]. For instance, a study has shown that the epidermal growth factor receptor (EGFR) exhibits decreased expression and phosphorylation of downstream signaling pathways in the epidermis. This decrease in EGFR activity suggests that RTK regulation in aging skin is complex and varies among different RTKs [49]. The molecular mechanisms of ROS involved in skin aging compared to normal mechanisms are illustrated in Figure 3 and Figure 4. Skin function and morphology were also declined by the accumulation of senescent cells. Although the basic mechanisms are still being elucidated, there is mounting evidence for the existence of disease-causing pathways leading to cutaneous aging. Extrinsic and intrinsic aging may occur simultaneously or concurrently. Genetic and epigenetic mechanisms control all these processes. Regulation of non-coding RNAs such as miRNA, long ncRNA, *etc.*, modification of histones and methylation of DNA are some of the mechanisms involved [11]. Meanwhile, miRNAs remain one of the most mysterious aspects in the study of aging biology, despite all the available data. The expression of certain miRNAs may serve as a biological indicator of aging, including photoaging, natural aging, and age-related disorders [3].

Interaction of the somatotrophic system and miRNAs in skin aging

The somatotrophic system, which encompasses the

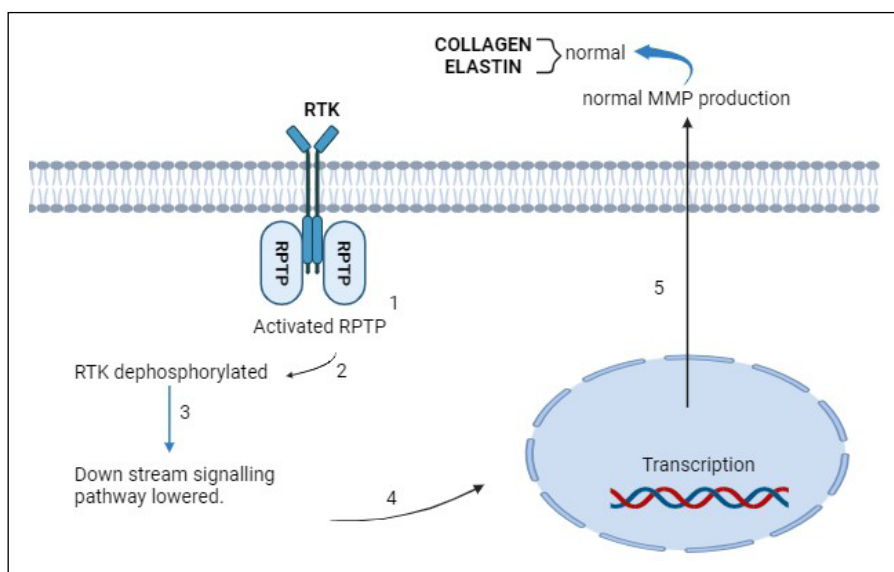


Figure 3. Formation of collagen and elastin in normal skin. (1) Under normal conditions, in the absence of ligands, receptor protein tyrosine phosphatase (RPTP) is activated. (2) It inhibits receptor tyrosine kinase (RTK) activity on the cell membrane by binding to it. (3) This dephosphorylated RTK downregulates the signaling pathway, leading to (4) transcription and (5) production of collagen and elastin.

somatotrophic axis and extrapituitary circuits, plays a crucial role in skin aging, especially in the context of congenital isolated growth hormone receptor deficiency (IGHD). IGHD, caused by a mutation in the GH-releasing hormone receptor (GHRH) gene, results in significantly reduced levels of GH and IGF-1, which are known for their cell proliferation and differentiation properties [50, 51]. Beyond the hormonal aspect, miRNAs have emerged as important regulators of metabolic changes associated with healthy aging. Our study hypothesized that GH deficiency in humans alters the abundance of circulating miRNAs, with a subset overlapping those found in GH-deficient mice [52, 53]. Among the significantly regulated miRNAs, hsa-miR-31, hsa-miR-146b, hsa-miR-100, hsa-miR-181b, hsa-miR-195 were of particular interest for their roles in aging-related pathways. *In vitro* assays confirmed that these miRNAs regulate the expression of age-related genes such as mTOR, AKT, NFκB, and IRS1, which are implicated in skin aging [52]. For instance, miR-181-5p was upregulated approximately sevenfold in IGHD humans, with an even more pronounced effect in older individuals. This miRNA inhibits cell proliferation, migration, invasion and tumorigenesis by targeting IGF-

1R and its downstream signaling pathways. Additionally, miR-181b-5p expression is increased in human senescent keratinocytes, indicating its tissue-specific properties and potential contribution to skin aging [52, 54]. These findings highlight the complex interaction between the somatotrophic system and miRNAs in resulting skin aging. This will provide new insights into research and enhancing skin health.

Role of microRNAs in general aging process

Aging is a complex phenomenon characterized by progressive degradation and reduced repair capacity of tissues and organs, leading to age-related pathological disorders. miRNAs regulate gene expression by repressing translation and play a key role in aging [11, 55]. Key miRNAs such as miR-34a and miR-29 promote cellular senescence, while miR146-a and miR-21 modulate inflammation [56]. Recent research has focused on miRNAs as biomarkers of aging in humans.

Role of microRNAs in skin aging and therapeu-

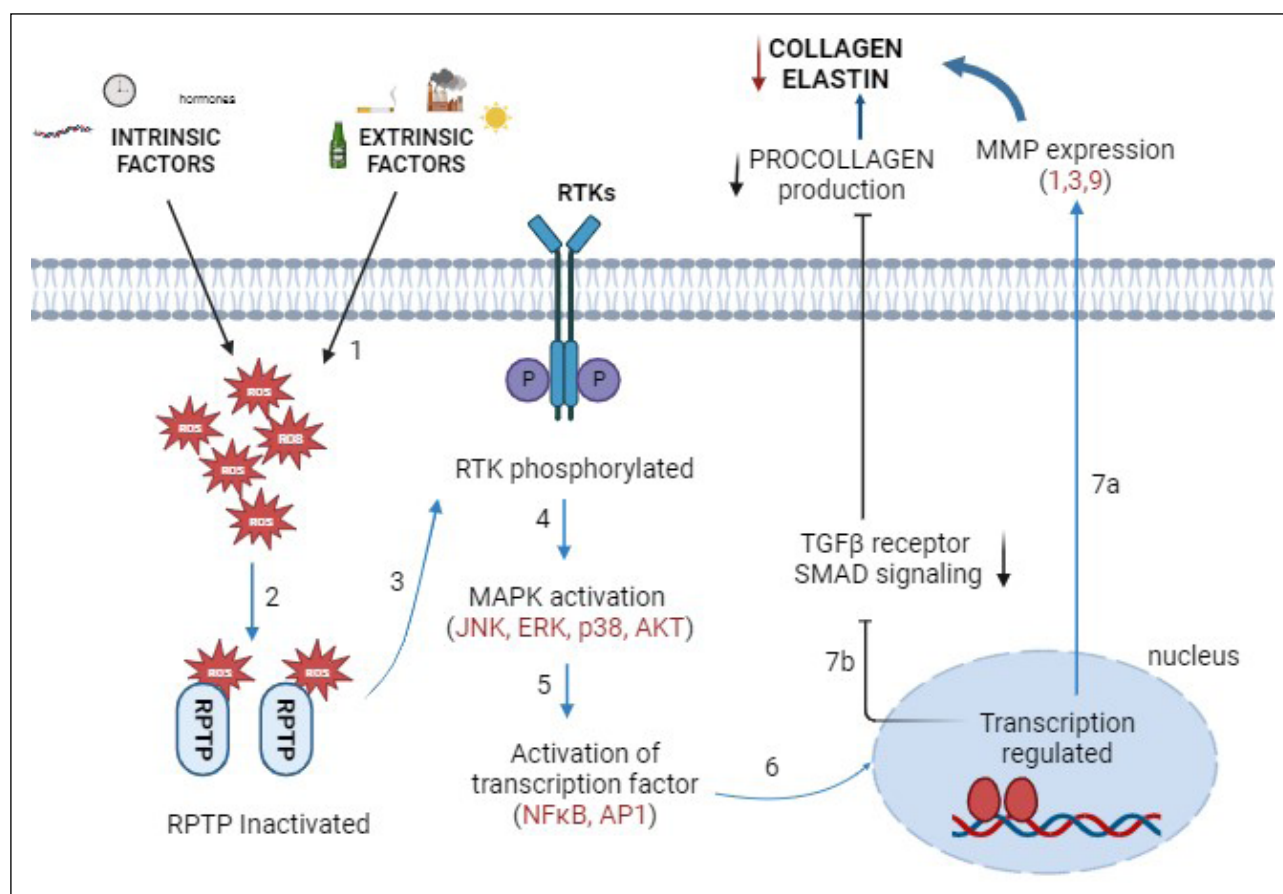


Figure 4. The pathway under the influence of intrinsic and extrinsic factors. (1) Intrinsic and extrinsic factors lead to the production of reactive oxygen species (ROS), which accumulate in the cell. (2) ROS inhibit RTPP by binding to the catalytic site. (3) RTK is phosphorylated and activated. (4) Activation of mitogen-activated protein kinases (MAPK) triggers other downstream signaling pathways, including extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), protein kinase B (AKT), and p38. (5) Nuclear factor κB and transcription factor activator protein-1 (AP-1) are then activated. (6) This regulates gene expression. Altered gene expression inhibits collagen synthesis in two ways. (7a) The expression of MMPs (MMP-1, 3, 9) is increased. Collagen production is decreased. (7b) Inhibition of TGF-β and SMAD signaling pathways. Decrease the synthesis of procollagen 1, which reduces collagen and elastin.

tic interventions

Short, single-stranded, non-coding RNAs are called microRNAs. They are about 25 nucleotides in length. These miRNAs regulate gene expression [14]. Several miRNAs have been found in both plants and mammals. It was first discovered in *Caenorhabditis elegans*, which is found in most eukaryotes, including humans. It is interesting to note that most studies show that many protein-coding genes are regulated by these miRNAs at the translational and transcriptional level. It is estimated that miRNAs account for about 1–5% of the human genome and control at least 30% of genes that code for proteins [55, 57–59]. However, the findings of Boehm and Slack reveal the role of miRNAs that regulate the age of *C. elegans* and establish the significance of miRNA in the skin aging process [60]. Furthermore, most miRNAs are synthesized from DNA sequences to become primary miRNAs, or pri-miRNAs, which are then processed to become precursor miRNAs, or pre-miRNAs, and ultimately mature miRNAs. miRNAs often decrease expression by interacting with the 3' UTR of target mRNAs [23]. However, there are also reports of miRNA interaction with other sites, including the 5' UTR, gene promoters, and the UTR at 5' region. Meanwhile, research has shown that miRNAs regulate the rate of translation and transcription by shuttling between various cellular compartments [61, 62]. Many biological processes depend on these regulators. Moreover, it is necessary for the normal growth in animals. Recent findings also revealed that miRNAs play a key role in regulating cutaneous aging and senescence. Many of the miRNAs were up- or down-regulated with aging at the tissue or organism level [11, 63]. In the context of the aging pathway outlined before, miRNA has the capacity to regulate various molecules. It provides additional control over the signaling cascade linked with ROS-induced aging. It is

interesting to note that the first investigation of miRNAs associated with aging in human epidermal keratinocytes revealed a set of regulated miRNAs [11].

miRNAs have the ability to regulate the levels of ROS either directly or indirectly. Moreover, it can regulate RPTPs, TGF- β and other proteins associated with redox homeostasis, as well as proteins like RTKs, AKT, MAPKs, *etc.*, thereby regulating the downstream signaling cascade. Redox homeostasis refers to the balance between the production and elimination of ROS in the cell. By targeting the mRNAs of these constituents, they can regulate ERK, JNK, *etc.* When miRNAs downregulate the expression of PTPs and other proteins, it will result in the accumulation of ROS, which leads to the breakdown of the ECM and the inhibition of procollagen 1. This will ultimately lead to the reduced production of collagen and the loss of structural and functional integrity of dermal tissues, which is a hallmark of aging [64]. Figure 5 depicts the involvement of miRNAs in the regulation of gene expression in skin biology at the post-transcriptional level (in various pathways).

It is an interesting fact that miR-668 and miR-137 were upregulated during organismal aging, which can also promote the aging of keratinocytes in humans [65]. The study conducted by Rivetti *et al.* finds that the upregulated miR-181 expression, miR-130, and miR-138 target sirtuin 1 (Sirt 1) and p63 mRNAs [66, 67]. It is suggested that sirt1 activity is important for replicative senescence of keratinocytes. On the other hand, p63 is actively involved in aging [66, 68]. Additionally, miR-191 inhibits the G1-S phase transition, which results in cell cycle arrest. This quiescent stage contributes to the aging process. MiR-152 can drastically reduce dermal fibroblast adhesion by suppressing integrin alpha 5, a signaling protein involved in cell surface-mediated processes [13]. Moreover, activation of p53, MAPK, and several other signaling pathways is caused by decreased levels of miR-106 and miR-17

Table 1. miRNAs that affect different skin cells which leads to skin aging.

miRNAs	Cell types affected	Up/Down regulated	Species (Human/Mouse)	Reference
miR-124	UV radiation induces this in keratinocytes	Upregulated	Human	[74]
miR-23a	Keratinocytes and fibroblasts	Upregulated	Human	[73]
miR-779	Langerhans cells	Upregulated	Mouse	[11]
miR-365	Fibroblasts	Upregulated	Human	[11]
miR-124	Keratinocytes	Upregulated	Human	[74]
miR-142	Melanocytes	Altered	Human	[74]
miR-9	Langerhans	Upregulated	Mouse	[11]
miR-25	Melanocytes	Upregulated	Human	[11]
miR-151a-5p	Langerhans cells	Upregulated	Mouse	[75]
miR-20a	Langerhans cells	Upregulated	Mouse	[11]
miR-106a	Fibroblast	Downregulated	Human	[11, 76]
miR-148a	Primary human fibroblast	Upregulated	Human	[76, 77]
miR-574-3p	Senescent fibroblast	Upregulated	Human	[11]
miR-93	Epidermis	Upregulated	Human	[11]
miR-146a	Fibroblast	Downregulated	Human	[13, 76]
miR-191	Keratinocytes	Upregulated	Human	[13, 78]
miR-29a	Fibroblasts	Upregulated	Human	[13, 79]
miR-181a	Keratinocytes/fibroblasts	Upregulated	Human	[72]
miR-155	Fibroblast	Downregulated	Human	[67, 80]

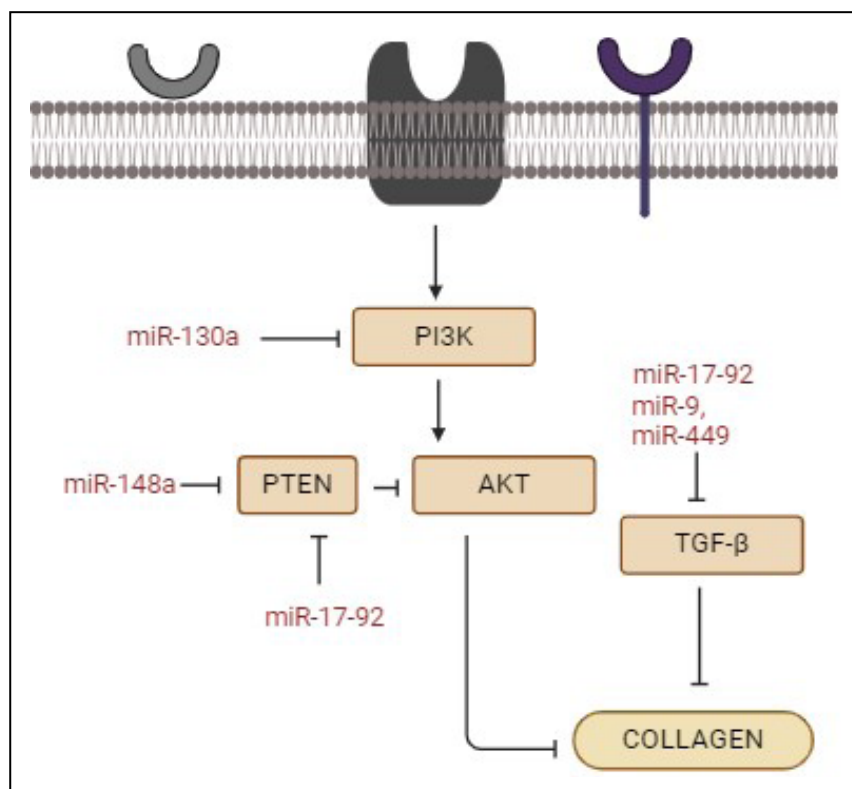


Figure 5. The role of different miRNAs in various signaling pathways leading to downregulation of collagen synthesis. PI3K, AKT, PTEN, and TGF- β are shown to be inhibited by different miRNAs, which in turn inhibit collagen synthesis.

in aged dermal fibroblasts [69]. Taken together, specific miRNAs have the ability to hinder the normal aging of cells by promoting cell proliferation. The expression of miRNA is modified when the skin is exposed to UV light for a long time, the levels of miR-27a, miR-145, miR-383, and miR-1246 are elevated, while those of miR-155, miR-663b, miR-3648, and miR-6879 are reduced [70]. Meanwhile, UVA radiation downregulates miR-155, which causes c-Jun to be upregulated. This influences the activity of the collagen gene in human fibroblasts [71]. Premature aging is the main result of photoaging. Human dermal fibroblasts are more sensitive to solar radiation than epidermal keratinocytes.

Conditions like diabetic foot ulcers, pressure ulcers, and venous leg ulcers contribute to skin aging by causing chronic inflammation, tissue damage, and impaired healing processes. These ulcers lead to persistent open wounds that disrupt the skin's barrier function, making it susceptible to further damage and infection. The chronic inflammation associated with these conditions accelerates the breakdown of collagen and elastin which maintain skin structure and elasticity. This will significantly impact overall skin health [72]. Research on miRNAs highlights their critical role in skin aging and diseases like chronic wound healing in the elderly. Key miRNAs such as miR-21, miR-31, and miR-203 promote keratinocyte functions essential for wound healing, while miR-29b, miR-98, and miR-185 regulate collagen production and scar formation. These findings suggest that miRNA-based therapies could enhance chronic wound healing and reduce scarring, making them valuable in managing skin aging-related conditions [73]. Some miRNAs and their roles in dermal aging

are shown in Table 1. Meanwhile, the therapeutic potential of miRNAs in skin aging is an evolving and active area of research today.

miRNAs play a crucial role in the aging characteristics of various skin appendages, such as hair follicles, sebaceous glands, and sweat glands other than above mentioned cells. Hair follicles containing hair papilla, matrix, root sheath, and bulge, have distinct compositions. miR-191 is involved in keratinocytes senescence in hair follicles by regulating CDK6 and SATB1, thereby influencing cell cycle progression and chromatin remodeling [11, 81]. Sebaceous glands, essential for skin lubrication and protection, are influenced by key signaling pathways such as Wnt, c-Myc, *etc.*, and their development is closely linked to hair follicle stem cells. Aging affects the sebaceous gland through changes in miRNA expression, like miR-338-3p and miR-574-3p, which impact lipid synthesis and inflammation, leading to altered skin barrier function [11, 82]. Similarly, sweat glands—the appendages for thermoregulation and fluid balance—are categorized into eccrine and apocrine glands. These glands, which are widely distributed except in specific areas, consist of a coiled secretory portion and a duct. The development and regeneration of sweat gland involve signaling pathways, including ERK, Wnt, *etc.*, which regulate cell growth and differentiation. Aging impacts sweat gland function through changes in miRNA expression, such as miR-29 and miR-141, which affect sweat production and require further research to understand and mitigate the age-related decline in sweat gland activity [11, 82, 83]. Understanding these miRNAs related to aging processes may help to develop treatments to maintain skin health and combat aging.

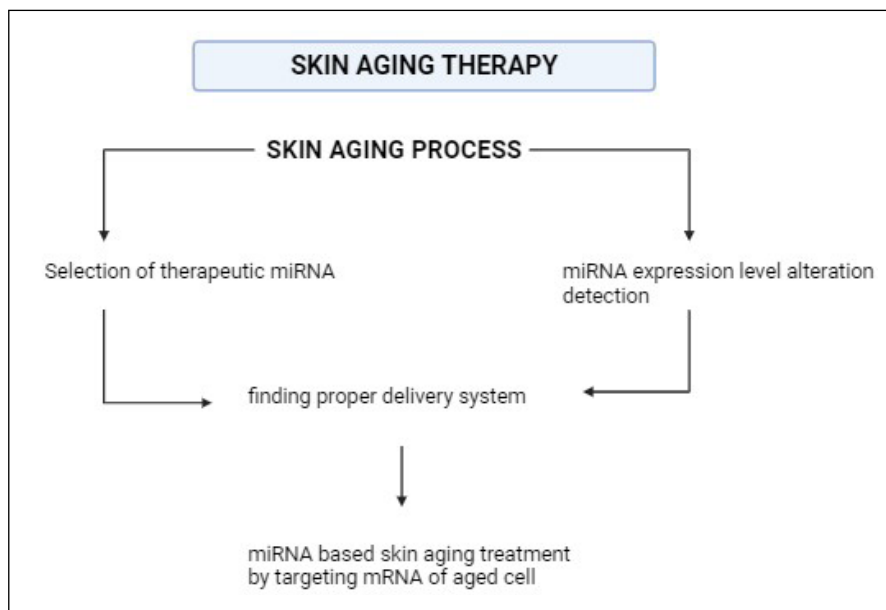


Figure 6. miRNA-based therapy. Identification of miRNAs whose expression levels are altered during aging. A suitable therapeutic miRNA is also selected. Then, using a suitable delivery system, the miRNA is transferred to the aged cell by targeting the mRNA.

Therapeutic interventions in anti-aging are aimed at preventing or slowing aging or the effects of aging. Beyond aesthetic concerns, skin aging is linked to several factors of physical health and overall quality of life. Therefore, anti-aging therapy is essential and contributes to a high quality of life. Many miRNAs have become universal regulators of a variety of skin conditions and can function as potential therapeutic targets and novel biomarkers of disease etiology and pathogenesis [2]. MiR-29, miR-124, and miR-152 are involved in the generation and regulation of collagen synthesis. Numerous studies have shown that increased levels of miR-29 inhibitors increase elastin mRNA and protein levels *in vitro* or *in vivo*. Several studies have shown that miR-29 increases the concentration of MMPs and thereby decreases collagen synthesis. Hence, increasing the expression of collagen, fibrillin, and elastin in skin fibroblasts results from suppressing miR-29 with an miR-29 antagonist. Such research may lead to the development of very potent cosmetic treatments to stop the aging process of the skin [84, 85]. Therefore, modulation of their function could influence the ability of the skin to maintain its integrity and strength. Thus, they can be considered as novel biomarkers and therapeutic targets. miRNAs have a greater significance in anti-aging mechanisms as they are essential for the molecular regulation of several aging-related processes [86, 87]. A study by Wing-fu Lai *et al.* describes the evidence of age-associated changes in miRNA expression, which highlights the potential of miRNA as a target and tool for anti-aging therapy [88]. Further research on miRNA finds that miR-101 helps modulate senescence induced by UV-B radiation, and another research shows that miR-146a inhibits UV-induced aging by targeting smad-4 [73]. Anti-aging treatment is an ongoing research area and miRNA is of great importance in it. Silencing gene expression by using miRNAs is one method to reduce skin aging. Figure 6 shows a miRNA-based method for skin aging therapy. Modification of miRNA expression is emerging as a valuable focus in the

cosmetic area, offering potential for the development of skin care products [73, 89]. Current research is shedding light on the molecular mechanisms behind several aspects of aging, including the connection between some aging processes and individual gene activity. Thus, by inhibiting these undesirable gene activities, miRNAs may be utilized to create new cosmetic designs and products, especially for skin care purposes like anti-aging. The expression of tyrosinase, an enzyme essential for melanin synthesis, can be reduced using miRNAs. This technique is a new and practical method for skin whitening [84, 90, 91]. Research on miRNA and anti-aging is still ongoing, and a deeper knowledge of the regulatory network is needed to develop targeted and efficient therapies.

Conclusions

Skin aging is a complex and integral phenomenon. It consists of 2 types: intrinsic and photoaging (extrinsic). Intrinsic aging is primarily caused by genetic factors, while extrinsic aging is caused by environmental factors. Intrinsically aged skin shows smooth, thin, sagging, pale morphology, while extrinsic aging mainly affects exposed areas, such as the neck, face, *etc.* Deep wrinkles, changes in pigmentation, roughness, *etc.* are the main features of photoaging. The commonly known skin-aging mechanism is the degradation of collagen by MMPs due to the accumulation of ROS. Skin aging is characterized by interconnected processes at the cellular, molecular, and organ levels. Despite ongoing research, the identification of distinctive biomarkers for aging remains a topic of exploration. In this review, we focus on the role of miRNA in skin aging. We have explained the current knowledge on miRNA's roles in molecular pathways and an insight into the therapeutic functions. MiRNAs play an important role in cellular and molecular functions of the skin due to their ability to control the expression of genes after transcrip-

tion. Their complex regulatory roles in skin aging and dermatology make them attractive biomolecules for further study and potential therapeutic intervention. However, the main problem or challenge in this therapeutic intervention today is the knowledge of the molecular mechanisms of aging. Further research on miRNAs linked to skin aging will include the discovery of new targets and their roles. Moreover, it will provide information on the regulation of aging mechanisms at the cellular and molecular levels. Investigating miRNAs as biomarkers of skin aging and exploring their role in diagnosis and prognosis is the main future scope of this study. By focusing on these perspectives for future research, researchers can expand their knowledge in this area. This, in turn, may open avenues for effective therapeutic interventions to maintain skin health and reduce the effects of aging.

Declarations

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