J. Cosmet. Sci., 64, 455–468 (November/December 2013)

Use of small RNA as antiaging cosmeceuticals

PINGJING ZHANG, JIANXIN CHEN, TIEJUN LI,
and YORK YUANYUAN ZHU, *Biomics Biotechnologies Co. Ltd, Economic & Technology Development Area, Jiangsu, The People's Republic of China 226016, and Small RNA Technology and Application Institute, Nantong University, Economic & Technology Development Area, Jiangsu, The People's Republic of China 226016.*

Accepted for publication May 17, 2013.

Synopsis

Over the past two decades, RNA interference (RNAi) has achieved great improvements in medicine, which has benefited the development of innovative cosmeceutical products, particular, to antiaging cosmeceuticals. A variety of ongoing research has tried to employ small RNAs—small interference RNA and microRNA as new cosmeceutical ingredients. Furthermore, several skin care companies have released new small RNA products in cosmetic market. In this review, we will describe the latest and most advanced approaches and strategies of using small RNA as antiaging cosmetics, including investigations on aging-related genes that small RNA target, method of delivering them, and challenges in the development of RNAi-based therapeutics for skin care cosmeceuticals. It is certain that advancement in this direction will evolve a new landscape for innovative antiaging cosmeceuticals.

INTRODUCTION

Modern society is increasingly integrated across national borders, and the global economy has augmented consumer access and individual buying power exponentially. In addition, advances in medicine have led to a trend of increasing life expectancy. The combination of these factors has resulted in the establishment and growth of the personal care market (1). Dr. Albert Kligman originally coined the term cosmeceutical and defined it in 1984 as a formulation that is used to improve the appearance of skin, but not for therapeutic purposes (2). Today, cosmeceuticals have become the fastest growing sector of personal care industry (3). Skin care companies have been continuously releasing new and innovative products that promise to transform the appearance of aging skin (4). A number of topical cosmeceutical treatments for conditions such as photoaging, hyperpigmentation, wrinkles, and hair loss have come into widespread use (5).

Over the past two decades, advancement in cosmeceuticals has generated a variety of strategies for antiaging treatment, including applications of recombinant proteins, peptides,

Address all correspondence to Pingjing Zhang at frank@biomics.cn.

natural bioactive compounds, herbal products, and many others (6). More recently, development in new cosmeceutical products has benefited from applications of newly advanced technologies such as RNA interference (RNAi). Today, a great deal of antiaging research has focused on the use of small RNA for improved appearance of aging skin as well as against hair loss (7). In this review, we will focus on recent progress in research and development of using small RNA in antiaging cosmetics, including investigations on aging-related genes that small RNA target, method of delivering them, and challenges in the development of RNAi-based therapeutics for skin care cosmeceuticals.

CHARACTERISTICS OF AGING

Skin aging is a complex biological phenomenon consisting of two components; aging caused by the genes we inherit is called intrinsic aging, the other type of aging is known as extrinsic aging and is caused by environmental factors. The process of intrinsic skin aging is thought to involve decreased proliferative capacity leading to cellular senescence and altered biosynthetic activity of skin-derived cells (8). Extrinsic aging, more commonly termed as photoaging, also involves changes in cellular biosynthetic activity but leads to gross disorganization of dermal matrix. With advancing age, the dermal/epidermal junction becomes relatively flat resulting from retraction of the epidermal papillae as well as microprojections of basal cells into the dermis. This flattening results in a more fragile epidermal/dermal interface and, consequently, the epidermis is less resistant to shearing forces. The three-dimensional arrangements of collagen and elastic fibers show marked alterations with age. Both fibrous components appear more compact because of a decrease in spaces between the fibers. Collagen bundles appear to unravel, and the individual elastic fibers show signs of elastosis (9). Skin aging leaves visible signs on the surface of skin and physical properties of the skin are modified. The most obvious clinical impression of elderly skin comes from increased formation of wrinkles and deficits in elasticity, another evidence of increasing age includes irregular dryness, dark/light pigmentation, sallowness, severe atrophy, telangiectases, premalignant lesions, laxity, and leathery appearance (10). Functional changes in the skin of elderly persons include a decreased growth rate of epidermis and hair (11).

Both intrinsic and extrinsic factors may conspire to hair aging. Intrinsic factors are related to individual genetic and epigenetic mechanisms with individual variations, whereas extrinsic factors include ultraviolet (UV) radiation, air pollution, smoking, and nutrition (12). Extrinsic factors insults to the fiber that induce hair weathering and fraying (13). The aging of follicles caused by intrinsic factors manifests as decrease of melanocyte function (graying) and decrease in hair production (alopecia) (14).

MECHANISM OF RNA INTERFERENCE

In the late 1990s, a landmark study demonstrated that gene expression could be inhibited by an introduction of double-stranded RNA with a sequence complementary to the gene being targeted, a mechanism that was referred to as RNAi (15). The importance of this work was well recognized by the 2006 Nobel Prize in physiology or medicine.

microRNAs (miRNA) and small interference RNAs (siRNA) are classes of regulating small RNA molecules, ranging from 18 to 24 nucleotides in length. They function by altering the stability or translational efficiency of messenger RNAs (mRNAs) with which they share sequence complementarity, as shown in Figure 1, and are predicted to affect up to one-third of all human genes (16).

RNAi-based therapeutics has recently emerged for treatment of cancer, infectious diseases, and other diseases associated with specific gene disorders. Since the discovery of RNAi, there have been more than 30 clinical trials involving 21 different biological drugs known as siRNA or miRNA (18). In principle, the RNAi mechanism elicits a posttranscriptional gene silencing phenomenon capable of inhibiting specific gene function with high potency at a few nanomolar dosages. The molecular mechanisms underlying some aspects of aging are now being unraveled, certain aging processes are associated with personal gene activities (8,19–21).

Therefore, small RNA agents could potentially be used to develop new cosmetic designs and products by suppressing those unwanted gene activities, in particular for skin care such as aging prevention (22) (Table I).

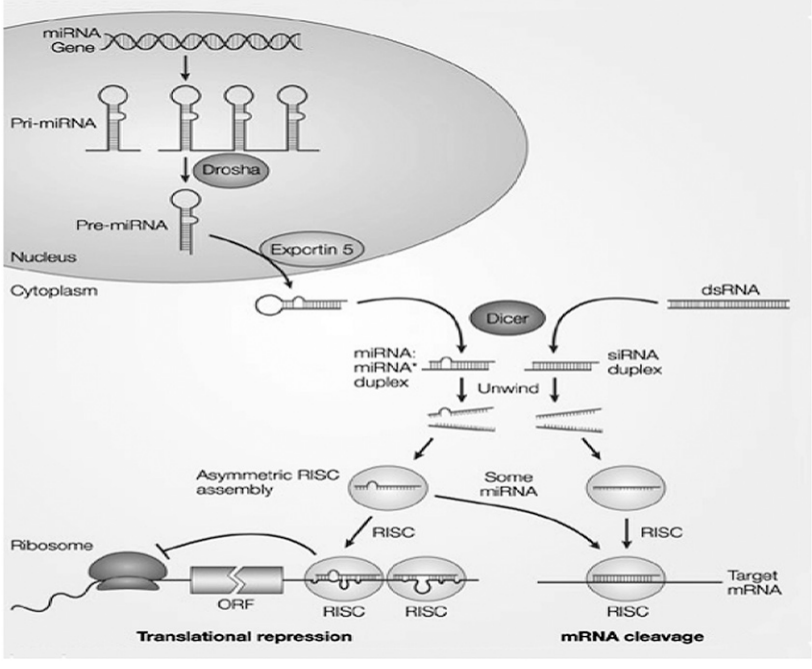

Figure 1. General mechanism for miRNA and siRNA (from Ref. 17).The nascent pri-microRNA (pri-miRNA) transcripts are first processed into ~70-nucleotide pre-miRNAs by Drosha inside the nucleus. Pre-miRNAs are transported to the cytoplasm by Exportin 5 and are processed into miRNA: miRNA* duplexes by Dicer. Dicer also processes long dsRNA molecules into small interfering RNA (siRNA) duplexes. Only one strand of the miRNA:miRNA* duplex or the siRNA duplex is preferentially assembled into the RNA-induced silencing complex (RISC), which subsequently acts on its target by translational repression or mRNA cleavage, depending, at least in part, on the level of complementarity between the small RNA and its target. ORF, open reading frame.

Table I
Small RNA in Antiaging Cosmeceuticals

Type of small RNA	Gene target	Application	References
miRNA	Tyrosinase	Whitening	23,24
siRNA	MITF	Whitening	25,26
siRNA	P53	Whitening	7
miRNA inhibitor	miR-29	Antiwrinkle	27,28
miRNA	Hyaluronidase	Moisturizing	19
siRNA	Androgen receptors	Hair care	29,30
siRNA	Tbx21	Hair care	31
miRNA inhibitor	miR-31	Hair care	32
miRNA	LSD1/2, DNMT1, MECP1/2	Antiaging	33

SMALL RNA IN SKIN WHITENING COSMECEUTICALS

There are many pigmentary disorders that pose cosmetic problems in humans. Melasma, freckles, and aging spots are among the most common ones (34). The number and amount of melanocytes, as well as the type and distribution of melanin in skin, are main factors affecting the color of skin. Synthesis of melanin pigment is completed by a series of oxidative reactions, along which tyrosinase (TYR) and microphthalmia-associated transcription factors (MITF) are the key regulators (35–37). TYR converts tyrosine to dihydroxyphenylalanine and further to dopaquinone; dopaquinone is subsequently autooxidized to dopachrome and, finally, to dihydroxyindole or dihydroxyindole-2-carboxylic acid to form eumelanin (38). Other major regulator in melanocyte development, function, and survival is MITF. MITF is thought to mediate significant effects of α-melanocyte stimulating hormone on differentiation by transcriptionally regulating enzymes that are essential to melanin production, i.e., TYR, tyrosinase-related protein 1 (TYRP1) and TYR-related protein-2 (TYRP2)/dopachrome-tautomerase (DCT) (39,40). Inhibition of TYR activity is still the most reported approach as a means of skin lightening. Other methods used include MITF inhibition, downregulation of melanocortin 1 receptor (MC1R) activity, interference with melanosomal transfer, and melanocyte loss (41).

Using miRNAs to target and reduce the expression of TYR presents a novel and feasible approach for achieving skin whitening. Chen *et al*. developed an artificial miRNA expression system which synthesizes miRNAs that downregulate TYR expression by binding and degrading TYR mRNAs. This anti-tyrosinase miRNA expression system successfully demonstrated the feasibility of miRNA-mediated skin whitening in mice and humans (23). Alternatively, novel siRNAs have been developed that specifically inhibited TYR expression, in which selected siRNAs exhibited such high activity that the siRNAs could be applied at a dose of less than 1 nM. Furthermore, the association of these TYR-specific siRNAs with cationic particles less than 1 μm in size makes it possible to significantly improve their penetration into target cells in a three-dimensional model such as skin (24).

In one clinical study, 31 patients with pigmented facial lesions were treated using a MITF siRNA (MITF-siR) cream that contained a highly efficient peptide-based transdermal vehicle (25,26). It demonstrated that MITF-siR silenced MITF gene expression effectively

and induced significant reductions in levels of TYR, TYRP1, and MC1R. The use of silencing MITF-siR led to significant inhibition of melanin synthesis and melanoma cell apoptosis. The results showed that, on treatment for 12 weeks, the patients treated with the MITF-siR cream were found to present significantly lighter hyperpigmented facial lesions than before the treatment; general improvement was first noted after four weeks' siRNA treatment. At the end of the treatment, clinical and colorimetric evaluations demonstrated 90.4% lightening of the siRNA-treated lesions toward normal skin color. The relative melanin contents in the lesions and adjacent normal skin after the treatment with the MITF-siR formulation were decreased by 26% and 7.4%, respectively. This treatment represents a safe and effective therapy for melasma, suggesting that siRNA-based agents could be developed for antiaging cosmeceuticals.

In another study, tumor suppressor protein p53 has been demonstrated to promote UVB-induced skin pigmentation by stimulating transcription of a melanogenic cytokine, proopiomelanocortin (POMC), in keratinocytes (42). Analyses revealed increased expression and phosphorylation of p53 in the epidermis of hyperpigmented spots, accompanied by higher expression of melanogenic cytokines, including stem cell factor, endothelin-1, and POMC. The involvement of p53 in hyperpigmentation was also indicated by significantly higher expression of p53 transcriptional targets in the epidermis of hyperpigmented spots. The *in vivo* data in UVB-exposed mouse skin showed that intradermal injection of p53-specific siRNA significantly suppressed the expression of mRNAs and proteins encoding paracrine cytokines as well as melanogenic factors (7). This knockdown resulted in the inhibition of hyperpigmentation. Taken together, these data revealed the essential role played by p53 in hyperpigmentation of skin via regulation of paracrine-cytokine signaling, both in keratinocytes and melanocytes.

SMALL RNA IN ANTIWRINKLE COSMECEUTICALS

If aging skin were a Broadway production, then facial wrinkling would get top billing among the large cast of benign clinical signs appearing in the show (43). There are several types of facial wrinkles classified with consideration to their location, pattern, histology, and etiology (44). Recent investigations showed that the dermis plays a decisive role, at least for skin aging caused by UV radiation. Exposure to UV radiation results in the accumulation of damages to the mitochondrial DNA of dermal fibroblasts and thus an altered gene expression in the affected cells, which chronically drives both the dermal and epidermal aging process (45–48). Aged dermis has fragmented elastic fibers, decreased collagen, and disproportionate types I and III collagens. This damage is attributed to several types of enzymes known as matrix metalloproteinases (MMPs) (49). Activation of MMPs can result in production of collagenase, elastase, gelatinase, and stromelysin (38,50).

miRNAs, the most studied small noncoding RNAs, play an important role in many biological processes by regulation of gene expression. Recently, miRNAs have been found to participate in the complex networks of cellular senescence and contribute to aging (51). Several investigations revealed that miR-29 members were upregulated in both elderly and senescence-model mice (52–54). Functional analysis showed that the transcriptional activation of miR-29 was triggered in response to DNA damage and occurred in a p53-dependent manner (55). The tumor suppressor p53 protects genome by promoting

repairs of potentially carcinogenic lesions in DNA. Meanwhile, p53 eliminates or arrests proliferation of damaged or mutant cells by processes of apoptosis and cellular senescence (56). These studies implicated a delicate balance between the tumor-suppressing and age-promoting functions by p53 (57).

Reduction of elastic fibers and collagen protein is another essential factor in formation of wrinkles (58). Several investigations showed that overexpression of miR-29 repressed, whereas miR-29 inhibitors increased, levels of elastin mRNA and protein *in vitro* or *in vivo* (59,60). Indeed, miR-29 conserved seed sequences were found not only in tropoelastin but also in collagen (61). A number of reports have demonstrated that use of miR29 inhibitors could lead to increased levels of collagen (62,63). Other data also showed that oxLDL resulted in upregulation of miR-29b expression in a dose-dependent manner *in vitro* and subsequently increased levels in MMP-2/MMP-9 enzyme activities (64). Because an increase in MMP activity has been linked to decreases in levels of collagen and elastin, a suitable strategy could be developed to manipulate the expression of miR-29 via an RNAi approach, by which this may offer a therapeutic opportunity against skin aging.***

Clinical studies demonstrated that there were significantly higher levels of miR-29 in the skin from older donors compared to that from younger ones (27). Suppressing miR-29 by miR-29 antagonist was shown to lead to an increase in collagen, fibrillin, and elastin expression in skin fibroblast. Such finding could perhaps be used to develop highly effective cosmetic solutions to reverse the process of skin aging (28).

SMALL RNA IN MOISTURIZING COSMECEUTICALS

With an adequate amount of water in the stratum corneum, the skin maintains its barrier function, feels soft and flexible, and looks smooth and healthy. Age, sun exposure, and dehydration are the main factors responsible for decreased skin elasticity (65). Moisturizing cosmeceuticals have a beneficial effect on prevention and treatment of dry skin by enhancing natural functions of the skin.

Hyaluronidase has recently drawn researchers' attention. Hyaluronic acid is distributed in skin's connective tissue and is one of the components in a water-retaining matrix. Hyaluronidase is a mucopolysaccharase that hydrolyzes glycosaminoglycans including hyaluronic acid. Thus, a reduction in the amount of hyaluronic acid by the hydrolysis could disable it from binding collagen and elastin molecules (66). This prevents formation and retention of new collagen and elastin and causes premature wrinkling and sagging (67). When a decrease in the level of hyaluronic acid occurs under such conditions as hyaluronidase activity is increased, moisture and tension of the skin are reduced (68). Therefore, hyaluronidase inhibitors are deemed useful cosmeceutical ingredients as they have antiaging effects on skin (69).

Tan *et al*. reported that silencing of hyaluronidase gene *Hyal* by RNAi resulted in reduced degradation of extracellular matrix where hyaluronic acid was present (70). In a separate study, Lin *et al*. discussed a potential role of siRNA as a novel therapeutic agent for dry skin (22). They redesigned the seed sequence of mir-434-5p, which was found or considered to be the only miRNA that targets both *Tyr* and *Hyal* genes in human, to form a highly matched region that binds to either TYR gene (*miR-Tyr*) or hyaluronidase gene (*miR-Hyal*). Interestingly, the targeted *Hyal* genes were knocked down specifically by

transfective expression of *miR-Hyal* in mouse skin (67% reduction) without any crossover off-target effect.

SMALL RNA IN HAIR CARE COSMECEUTICALS

The most common types of hair growth disorders are caused by aberrant hair follicle (HF) cycling. One such disorder is androgenetic alopecia, characterized by a shortening of the anagen phase and prolongation of telogen combined with miniaturization of HF (71). Androgens, which play a key role in androgenetic alopecia, have been identified in people with this condition. Studies demonstrated that variations in the androgen receptor gene led to increased activity of androgen receptors in HFs. As a result, current pharmacological therapies for hair disorders include a range of antiandrogens that block the intracellular androgen receptors (72). A promising line of studies has been completed by Kerner and colleagues who proposed modulating androgen receptor expression with RNAi for hair and skin therapy (29,30). It becomes clear that RNAi technology could be applied for treating androgenetic alopecia to modulate genes that are involved in hair loss in a highly specific manner.

Alopecia areata is also an autoimmune disease affecting HFs, resulting in hair loss. This was thought to be triggered by a collapse of immune privilege. Nakamura *et al*. suggested an involvement predominantly by Th1 cells in alopecia lesions (31). Therefore, they established a gene therapy experiment in an alopecia areata C3H/HeJ mouse model focusing on *Tbx21* gene that plays a key role in Th1 cell development. Topical application of siRNAs conjugated to a delivering vehicle was found to result in a knockdown of the *Tbx21* gene and have a positive effect on symptoms of alopecia in C3H/HeJ mice, which in turn led to restoring of hair growth.

miRNAs, which play a critical role in skin morphogenesis, were also reported to be involved in regulation of HFs development and cycling, however, neither their expression nor their roles has been characterized yet (73). Recently, an investigation showed that the expression of miR-31 was markedly increased during anagen and decreased during catagen and telogen. Administration of an antisense miR-31 inhibitor into mouse skin during the early and mid-anagen phases of hair cycle resulted in accelerated anagen development and altered differentiation of hair matrix keratinocytes and hair shaft formation. Both *in vitro* and *in vivo* data suggested that miR-31 regulated negatively the expression of *Fgf10*, *Krt16*, *Krt17*, *Dlx3* genes as well as some keratin genes (32). Thus, by targeting a number of growth regulatory molecules and cytoskeletal proteins, miR-31 could be involved in establishing an optimal balance of gene expression in HF required for its proper growth and hair fiber formation.

SMALL RNA IN STEM CELL-BASED COSMECEUTICALS

Reversal of cellular senescence would be an important function of antiaging cosmeceuticals, thus many attempts have been undertaken to influence cellular senescence. The stem cell extract is known to have regenerative properties because of containing many cytokines and growth factors, which offers promising potential for preventing skin aging (74). However, there are ethical difficulties regarding the use of human embryonic stem cells (hESCs). One way to circumvent the issues is by the generation of pluripotent cells

directly from donor's own cells. Induced pluripotent stem cells (iPSCs) are cells that were originally from adult tissues, but have been forced to produce proteins that are thought to be essential for the pluripotency of hESCs. By making cells express embryonic stem cell proteins, such as Oct4, Sox2, Klf4, and c-Myc, iPSCs exhibited the essential characteristics of hESCs as confirmed by morphological and other molecular criteria (75).

miRNAs have been identified to play a critical role in the maintenance and renewal of hESCs. Recently, several investigations showed that a small noncoding RNA, called miR-302, can replace all previously defined proteins to reprogram human and mouse somatic cells to ESC-like iPSCs (76–78). It is demonstrated that miR-302 functions as a gene silencer and simultaneously downregulates multiple key epigenetic regulators, including lysine-specific histone demethylases 1 and 2 (LSD1/2), DNA (cytosine-5-) -methyltransferase 1 (DNMT1), and methyl-CpG binding proteins 1 and 2 (MECP1/2), which subsequently triggers the activation of stem cell factors Oct4 and Sox2 to complete the reprogramming process (33). The functions of miR-302 have provided a convenient means to control both quantity and quality of iPSCs, opening up a new avenue to application of stem cell facial. On the basis of RNAi technology to reprogram skin cells into stem cells, essential elements will be extracted for production of innovative cosmetic ingredient.

CHALLENGES IN TRANSDERMAL DELIVERY OF SMALL RNA

A variety of methods for delivery of RNA through skin have been demonstrated; however, effective patient-friendly delivery remains a major challenge to clinical utility of small RNA cosmeceuticals. In general, a topical application of cosmetic formulations requires a successful delivery of active ingredients through lipid barrier of skin to reach targeted lower layers without causing any irritation (79). However, it is difficult to introduce small RNA into skin by conventional methods. The obstacles lie in the highly lipophilic nature and barrier function of uppermost layer of skin, the stratum corneum, for instance, which restrict or prevent hydrophilic, high molecular weight and charged molecules such as RNAs from permeating into the dermis (80).

MICROPORATION TECHNOLOGY

To deliver successfully hydrophilic drugs or macromolecular agents of interest such as small RNA, many research groups and pharmaceutical companies have paid a great attention to the use of microporation methods and devices (80). In summary, microporation techniques include typically iontophoresis (81), electroporation (82), sonophoresis (83), and microneedle (84). They share a common goal of enhancing permeability through a biological membrane by creating transient aqueous transport pathways of micron dimensions across the membrane (80).

NANOTECHNOLOGY

Recently, much of ongoing research is focused on the use of nanotechnology to aid noninvasive transdermal delivery of novel small RNA therapeutics. Some progress toward

clinical applications has been achieved in several investigations. Ritprajak *et al*. proposed a new siRNA-based therapy using cream-emulsified CD86 siRNA, targeting DCs for murine contact hypersensitivity and atopic dermatitis–like disease (85). Topical application of CD86 siRNA reduced effectively antigen-specific local inflammation in mice skin. Wang *et al*. demonstrated that chitosan nanoparticles containing imiquimod and siRNA exerted an anti-inflammatory effect and may provide a new and simple therapy for asthma (86). In particular, researchers at Northwestern University have identified a way of delivering gene-regulating molecules through topical moisturizers (87). This important study on nanoparticle transdermal delivery demonstrated that spherical nucleic acid nanoparticle conjugates (SNA-NCs), which consisted of gold cores surrounded by a dense shell of highly oriented and covalently immobilized siRNA, penetrated freely almost 100% of keratinocytes *in vitro*, mouse skin, and human epidermis within hours after application. Applying SNA conjugates may offer a promising method for transdermal delivery of small RNA as therapeutics and cosmetics.

CELL-PENETRATING PEPTIDES

On the other hand, cell-penetrating peptides (CPP) have been increasingly used to mediate delivery of small interfering RNA nucleotides *in vitro* and *in vivo*. Application of CPP in topical and transdermal delivery systems has recently garnered a tremendous attention in both cosmeceutical and pharmaceutical research and development (88). A variety of studies reported that conjugation of peptide to siRNA led to enhanced absorption into skin and knockdown of corresponding protein targets (89–92). In particular, Yi *et al*. demonstrated that conjugating TD1 to R8 covalently can be a powerful way to deliver siRNAs into epidermis and dermis of mammals (25). High efficacy of the MITF-siR cream formulation could be because of ionic interactions between R7 and siRNA aided by TD1, thus creating a transient opening in the skin to facilitate access of the siRNA to melanocytes. Indeed, such a noninvasive delivery of small RNA for skin whitening has been clinically tested with good efficacy (25,26).

SAFETY OF SMALL RNA COSMECEUTICALS

Natural RNAs have been used as cosmetic ingredients with a long history. Several cosmetic end products launched recently in the market contain natural RNA ingredients, such as sodium RNA or *Saccharomyces cerevisiae* extract. It is believed that natural RNA not only has a moisture retaining property derived from the nature of its high molecular anionic polymer but also has a UV-preventing property derived from its chemical structure (93,94). In addition, natural RNA is genetic material and has some unknown antiaging benefits (95). With these properties, RNA has generally been considered safe for use as a functional ingredient for a long time.

Besides having a specific gene target, small RNA is different from natural RNA in several aspects, such as length of oligonucleotide and effective dosages. Small RNA is chemically synthesized and may induce toxicities such as activation of innate immunity as well as off-target gene silencing. In general, double-stranded RNA can induce cellular changes through induction of interferons and other cytokines by the innate immune

system (96–98). The interferon response is especially obvious for duplex RNAs greater than 30 bases long. At a dose less than 1 nM, the dose-dependent interferon response to small RNA could be negligible. In a design of small silencing RNA, avoiding certain sequence motifs can reduce interferon responses, and immunostimulatory aspects from small RNAs can be further reduced through chemical modifications of nucleotides (97,98). Although other safety concern such as "off-target" effects that small RNAs may pose (i.e., unintended alteration of nontarget gene expression), designing modified small RNA to maximize selectivity while retaining potency could minimize the off-target effects (99). In summary, toxicities from the use of small RNA could be minimized by better designs to avoid immunostimulatory motifs and to reduce amounts required for efficacy through more selective delivery to desired tissue or target genes.

To date, several studies have demonstrated that small RNA is safe for cosmetic applications. Zheng *et al*. reported that there was no clinical or histological evidence of toxicity on the small RNA–treated skin. No cytokine activation in mouse blood or tissue samples was observed, and after three weeks' of topical skin treatment, the SNA structures were virtually undetectable in internal organs (87). Similarly in the Valentine's study (100), it was believed that small RNA formulation had no significant skin irritation. No histopathological alterations in the skin of the animals treated with either nanodispersion incorporating small RNA or naked small RNA were observed at 48 h post application. No significant difference was observed in the epidermal thickness after treatment with the nanodispersions compared to saline-treated animals. In a clinical study of topical application, neither toxicity nor serious side effect had been observed on use of MITF-siR that was chemically synthesized and modified (25,26).

PERSPECTIVES ON ANTIAGING SMALL RNA COSMECEUTICALS

Cosmeceuticals are the fastest growing sector in the cosmetic industry and the future of antiaging cosmeceuticals in particular is very promising. Nowadays, the major remaining challenges of small RNA cosmeceuticals are to elucidate molecular mechanisms of aging and to develop safe and effective noninvasive transdermal delivery. As scientists continue to search for breakthroughs, in-depth understanding of biological pathways that distinguish young and aging skin continues to provide new insights into the process of skin aging, which will in turn lead to better preventive measures and antiaging treatments. We believe that cosmeceuticals in the antiaging field will be flourishing in the future through applications of sound science and advanced technologies, including RNA interference, nanotechnology, biomimicry in cosmetics, stem cell technology, novel extraction techniques, and advances in biopolymers.

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