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Biology of estrogens in skin: implications for skin aging

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Abstract: Estrogens have a profound influence on skin. The relative hypoestrogenism that accompanies menopause exacerbates the deleterious effects of both intrinsic and environmental aging. Estrogens clearly have a key role in skin aging homeostasis as evidenced by the accelerated decline in skin appearance seen in the perimenopausal years. Estrogens improve skin in many ways. Among these, they increase collagen content and skin thickness and improve skin moisture. However, despite the knowledge that estrogens have such important effects on skin, the cellular and subcellular sites and mechanisms of estrogen action are still poorly understood. Estrogen receptors (ERs) have been detected in skin, and recent studies suggest that estrogens exert their effect in skin through the same molecular pathways used in other non-reproductive tissues. Although systemic hormone replacement therapy (HRT) has been used for many years, recent trials have reported a significant increased risk of breast cancer and other pathologies with this treatment. This has led to reconsider the risks and benefits of HRT. For this reason, systemic HRT cannot be recommended today to treat skin aging. Currently, intensive research is conducted to develop new drugs called selective ER modulators (SERMs). These drugs exert mixed estrogenic and antiestrogenic effects depending on the tissue and cell type. One might expect in the future such a drug targeting specifically the skin without systemic side effects.

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Introduction

As the population of postmenopausal women increases, interest in the effects of estrogens grows. The influence of estrogens on several body systems and especially reproductive tissues, nervous and cardiovascular systems, and skeleton has been well documented. However, a less explored area is the effect of estrogens on skin. Estrogens affect several skin functions as hair growth (1–3), pigmentation (4–6), vascularity (7–9), elasticity (10), and water-holding capacity (11). Since its first use in the 1940s, systemic estrogen therapy has been known to have obvious, visible effects on the skin. In particular, observations have been made regarding the ability of estrogen to improve wound healing in postmenopausal women (12,13) and to combat the phenomenon of skin aging. However, despite the knowledge that estrogens have such important effects, the cellular and subcellular sites and mechanisms of estrogen action in skin are still poorly understood. In this article, we review the effects of estrogen on skin and particularly its ability to prevent skin aging. We also report the recent discoveries regarding the molecular mechanisms of estrogen effect in skin.

Estrogen effect on skin aging: clinical overview

The aging of skin occurs in all individuals at a variable rate that is influenced by genetic, environmental, and hormonal factors. This process can be divided into intrinsic and photoaging. Photoaging is the term given to the superposition of chronic sun damage on the intrinsic aging process (14). It describes premature skin aging in chronically photo-exposed skin and is characterized by severe wrinkling and pigmentary changes such as solar lentigo and mottled

pigmentation. Intrinsic aging or chronologic aging describes skin damage due to the passage of time and is characterized by smooth, pale, finely wrinkled skin and dryness (15). Estrogens prevent skin aging by influencing skin thickness, skin wrinkling, and skin moisture (16–21). Not just the skin but also skin appendages, such as hair, are influenced by estrogens (22). High levels of estrogen during pregnancy encourage hair growth (23), and hair loss has been associated with the onset of the menopause (24).

Estrogen effect on skin thickness and collagen content

Collagen is a main constituent of the skin and provides the major support for skin resistance. The most abundant type, collagen I, predominates in the reticular dermis and type III collagen in the papillary dermis as well as at sites of new collagen deposition. It was first noticed in 1941 by Albright et al. (25) that postmenopausal women with osteoporosis had skin that was noticeably atrophied. These observations were corroborated by Brincat et al. (26) when they demonstrated that there was a decrease in skin thickness and skin collagen content, corresponding to a reduction in bone mineral density, in the years following menopause, particularly in the initial postmenopausal years. They found an average linear decline of 2.1% of skin collagen and 1.13% skin thickness per postmenopausal year in the initial 15–18 postmenopausal years. More recently, Affinito et al. (27), using skin biopsy immunohistochemistry and computerized image analysis, showed that skin collagen decline was closely correlated to years following menopause. They showed that postmenopausal women had decreased amount of types I and III collagen as well as a decreased type III/I ratio in comparison with premenopausal women. Several controlled studies have also shown the estrogen effects on skin collagen or skin thickness (Table 1). Castello-Branco et al. (28) showed by skin biopsies an increase in skin collagen content of 1.8–5.1% with oral and transdermal hormone replacement therapies over 12 months. Callens et al. (29) studied the influence of different hormone replacement therapy (HRT) regimens on postmenopausal women using non-invasive techniques such as skin echography and found an increase in skin thickness of 7–15% in postmenopausal women utilizing an estradiol gel patch or estradiol transdermal system. Maheux et al. (30) studied postmenopausal nuns utilizing a randomized, double-blind, placebo-controlled study and showed that in the group treated with oral conjugated estrogens, there was a significant increase in skin thickness and skin dermis at the level of the greater trochanter as measured by ultrasonography and skin biopsy, respectively. As the skin is affected by lifetime sun exposure and smoking, the use of nuns in the study helped eliminate some of these confounding factors and focus on the effects of conjugated estrogens on chronologic aging alone. Using computerized image analysis of skin samples, Sauerbronn et al. (31) found an increase of 6.49% of collagen fibers in the dermis after 6 months of topical treatment with estradiol valerate and cyproterone acetate. Varila et al. (32) showed not only that topical estrogen increases the collagen content, as measured by skin hydroxyproline, but also that the estrogen causes an increase in collagen synthesis, as was apparent by the increase in the levels of the carboxyterminal propeptide of human type I procollagen and of the amino terminal propeptide of human type III procollagen.

Estrogen effect on skin moisture

The ability of the skin to hold water is related to the stratum corneum lipids which play a predominant role in maintaining the skin barrier

Table 1. Estrogen effects on skin collagen or skin thickness in human (results from controlled studies)

Study	Type of measurement	Hormones used	Results
Castelo-Branco et al. (28)	Skin biopsy analysis	Conjugated equine estrogens or transdermal 17β-estradiol	Increase in skin collagen of 1.8–5.1% after HRT for 12 months
Callens et al. (29)	Skin thickness measured by ultrasonagraphy	17β-estradiol gel or estradiol patches	Increase in skin thickness of 7–15%
Maheux et al. (30)	Skin thickness measured by ultrasonagraphy	Conjugated estrogen 0.625 mg	Increase in skin thickness by 11.5% after HRT for 12 months
Sauerbronn et al. (31)	Skin biopsy analysis	Valerate estradiol and cyproterone acetate	Increase in dermis collagen content of 6.49%
Varila et al. (32)	Skin biopsy analysis	Topical 17β-estradiol	Increase in hydroxyproline by 38% after treatment for 3 months

HRT, hormone replacement therapy.

function (33) and also to the dermal glycosaminoglycans which have a high water-holding capacity (34).

A large population-based cohort study demonstrated that postmenopausal women who were not taking HRT were significantly more likely to experience dry skin compared with those postmenopausal women taking estrogen (35). Pierard-Franchimont et al. (11) showed that transdermal estrogen therapy leads to significantly increased water-holding capacity of the stratum corneum as measured by the plastic occlusion stress test suggesting that estrogen may play a role in the stratum corneum barrier function. Denda et al. (36) demonstrated changes in the stratum corneum sphingolipids with aging and suggested a possible hormonal influence. Estrogens also affect dermal water-holding capacity: studies in animals (37) have demonstrated marked increases in glycosaminoglycans within 2 weeks of estrogen therapy, and studies in human (38) have shown estrogens to increase dermal hydroscopic qualities.

Estrogen effect on skin wrinkling

Wrinkles are modifications of the skin associated with cutaneous aging appearing preferentially on sun-exposed areas (actinic aging). Moreover, they can be increased by various intrinsic (heredity, ethnic, hormonal, and pathological) or extrinsic factors (irradiation, pollution, temperature, and humidity). Histological studies of wrinkles have shown alterations of dermal component with atrophy of dermal collagen, alterations of elastic fibers and marked decrease in glycosaminoglycans (39,40). In a double-blind, placebo-controlled study, Creidi et al. (41) showed that a conjugated estrogen cream applied to the facial skin of postmenopausal women resulted in significant improvement in fine wrinkles as clinically evaluated by dermatologists. Young et al. (42) reported that hypoestrogenism increases the risk for wrinkling in Korean women, and Dunn et al. (35) pointed out in their large cohort study that postmenopausal women using estrogen were significantly less likely to develop skin wrinkles. That study controlled for confounding factors such as age, body mass index, and sun exposure. As noted earlier, estrogens cause an increase in collagen (28) and glycosaminoglycans (37) in the dermis, which may explain the decrease in skin wrinkling with estrogen treatment. Decreased skin elasticity has been demonstrated in women after menopause (43), and changes in the skin elastic fibers have been reported after application of estriol ointments to the skin of postmenopausal women. These changes included a thickening of the elastic fibers in the papillary dermis. The elastic fibers were also noted to be in better orientation and slightly increased in number (44).

Estrogen effect on skin pigmentation

Skin pigmentation is determined by genetic, environmental, and endocrine factors, which influence both melanin synthesis in melanocytes and the distribution of melanin throughout the epidermis. Estrogens regulate skin pigmentation. An increase in cutaneous pigmentation due to increase in ovarian and/or pituitary hormones is common during pregnancy. Melasma, a well-characterized acquired pigmentation occurring exclusively in sun-exposed areas, is exacerbated by pregnancy and oral contraceptives (45,46). Variations of skin pigmentation with the menstrual cycle have also been reported and may result from synergistic action of estrogen and progesterone (4). Skin photoaging is associated with dyspigmentation such as solar lentigo and mottled pigmentation. Sun exposure is the main risk factor of this dyspigmentation. The role of endocrine factors and particularly estrogens in this process, if any, is unknown. There are few reports on the effects of topical estrogen application on pigmentary changes in photoaged skin. Creidi et al. reported no improvement in mottled pigmentation and lentigines (41). Schmidt et al. did not mention also any improvement in dyspigmentation. In contrast, side effects such as an increased pigmentation on the cheeks were observed in few patients (47).

Estrogen effect on hair growth

Hair growth encompasses three stages, all known to be influenced by estrogen: growing (anagen), structural regression (catagen), and resting (telogen) (48,49). High systemic estrogen levels during pregnancy prolong the anagen phase of the hair follicle, and the plummeting estrogen levels postpartum cause this excess number of anagen follicles enter telogen phase simultaneously, sometimes resulting in clinically significant hair loss, the so-called telogen effluvium (23). Androgenetic alopecia (AGA) also known as female pattern alopecia is the most common hair loss in women and is most frequently observed after menopause (24), suggesting a role

of estrogens or the estrogen to androgen ratio. AGA is a dihydrotestosterone (DHT)-mediated process, characterized by continuous miniaturization of androgen-sensitive hair follicles (50). Indeed, it is usually treated with systemic antiandrogens such as cyproterone acetate (51) in women, or steroidogenic enzyme inhibitors such as finasteride (52) in men. Topical estrogen is also used as treatment, especially in Europe (53). The mechanism involved in estrogen-mediated induction of hair growth in AGA is not well understood. Some studies have shown an increased anagen and decreased telogen rate after treatment as compared with placebo (54). Niiyama et al. have demonstrated the ability of estrogen to modify androgen metabolism in dermal papillae of hair follicle (55). They showed that estradiol diminishes the amount of DHT in human hair follicle by inducing aromatase activity, the enzyme responsible of conversion of testosterone to estradiol (56). The induction of aromatase activity increases the conversion of testosterone to estradiol, thereby diminishing the amount of testosterone available for the conversion to DHT which might explain the beneficial effect of estrogen treatment of AGA.

Molecular mechanisms of estrogen effects: overview

Estrogens regulate diverse cellular functions including proliferation, morphogenesis, differentiation, and apoptosis. The pathways by which estrogens influence cellular functions are complex.

The classical mechanism of estrogen action involves interactions with intracellular receptors, members of the superfamily of steroid receptors, and regulation of gene transcription. This genomic effect is characterized by its delayed onset of action and occurs within minutes to hours. In contrast, it is now appreciated that more rapid non-classical pathways of estrogen action also influence cellular function. Typically, these effects occur within seconds to minutes and are mediated by membrane receptors that are coupled to cytosolic signal transduction proteins.

Genomic estrogen effect

Estrogens mediate their activity by interaction and activation of specific intracellular receptor proteins, the estrogen receptors (ERs). Subsequently, the receptor–ligand complex binds to specific DNA sequences located within the regulatory region of the target genes. The steroid receptor complex then interacts with other cellular components to either activate or suppress transcription of the target gene in a promoter-specific and cell-specific manner (57) (Fig. 1).

The two nuclear estrogen receptors ER-α and ER-β. To date, two isoforms of nuclear ERs have been identified, cloned and characterized from several species: ER-α and ER-β (58–61). They are distinct proteins encoded by separate genes located on different chromosomes (62). The ER-α and ER-β proteins bind 17β-estradiol (E2) with nearly equal affinity and exhibit a very similar binding profile for a large number of natural and synthetic ligands (63). Isoflavone phytoestrogens daidzein and genistein are well-known ER-β-selective compounds (64). They bind and activate human ER-α and ER-β with an up to 100-fold stronger activation of ER-β (65). In many cells, the receptors coexist as either homodimers or heterodimers (66,67), but the distribution of the two receptors does not completely overlap. ER-α exists as the predominant receptor in most target organs (68). However, ER-β is prominently expressed in ovary, prostate,

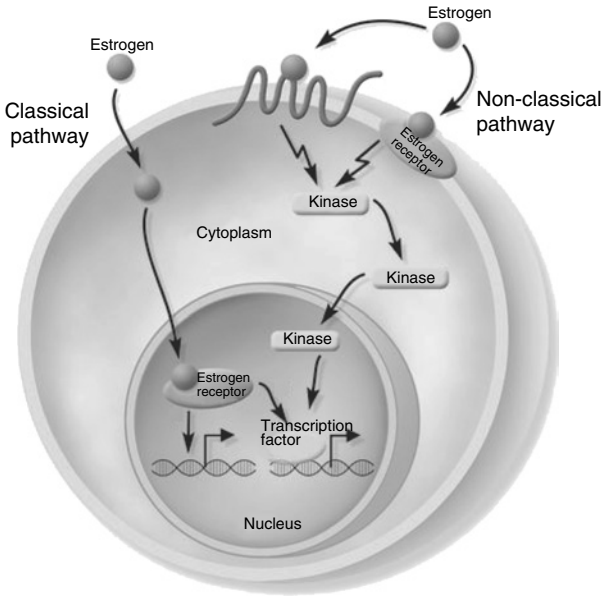

Figure 1. Estrogens can affect cellular function by a variety of mechanisms. The classical pathway depends on direct interaction of estrogen with its receptor in the nucleus. The non-classical pathways work more rapidly and depend on the ability of estrogen to interact with either membrane estrogen receptor or non-steroid hormone receptors as GPR30. The non-classical pathways activate mitogen-activated protein (MAP) kinases that ultimately regulate transcription of specific genes. Via these non-classical pathways, it appears that estrogens can also interact with other signaling pathways (131).

lung, and hypothalamus (69,70), and recent evidence indicates that there are specific actions of estrogen that can be attributed to one receptor but not the other (71–73).

Non-genomic estrogen effect

Strong evidence now exists for the presence of cell-surface forms of estrogen receptors that are coupled to cytosolic signal transduction proteins and contribute to the cell biological effects of estrogen (Fig. 1).

Membrane ER

More than 20 years ago, an estradiol-binding protein in cell membranes was identified (74,75). Subsequent work has begun to clarify the location, structure, and function of this binding protein in the cell plasma membrane (76–79). The membrane receptor has not been isolated or sequenced; hence, its precise molecular structure is still unknown. However, studies have shown that a variety of antibodies directed against multiple epitopes of nuclear ER-α also identify an endogenous membrane protein in several cell types (80). Such a membrane receptor, very similar to the nuclear ER-α, has been demonstrated in many cells including MCF-7 breast cancer cells (81), endothelial cells (82), osteoblasts (83), and neuronal cells (84). In addition, transfection of ER-α into cells that do not express the gene results in the production of both nuclear and membrane estrogen receptors (81). Therefore, it appears that the membrane receptor must be very similar to the nuclear receptor. The location of this receptor within the plasma membrane has been recently clarified: membrane ERs are located within caveolae (85,86), specialized membrane invaginations that are enriched in the scaffolding protein caveolin-1, and compartmentalize signal transduction (87).

It was also reported in breast cancer cells that estradiol interacts in the cell membrane with the G-protein-coupled receptor (GPCR) GPR30 to stimulate signaling and that this interaction does not require ER (88). These data appear to contradict previous studies and will require confirmation.

Signaling pathways activated by estrogen and implications for cell physiology

After estrogen binds membrane ER, the receptor–ligand complex activates several G proteins, which in turn trigger various signal transduction pathways. Thus, membrane ERs appear to be part of the large family of GPCRs.

An important non-genomic pathway for estrogen action is the stimulation of the extracellular-regulated kinase (ERK), which is a member of the mitogen-activated protein kinase (MAPK) family. The MAPKs are involved in the transduction of externally derived signals regulating cell growth, division, differentiation, and apoptosis (89). Rapid activation of this pathway by estrogen has been demonstrated in MCF-7 breast cancer cells (90), and this activation contributes to estrogen-induced proliferation (91) and survival (92) of MCF-7 cells. Kousteni et al. (83) showed that estrogen signaled through the same pathway, promoting survival of osteoblasts. ERK activation by estrogen also underlines the stimulation of nitric oxide production in endothelial cells leading to stimulation of angiogenesis (77). Recently, Kousteni et al. (93) reviewed the differences in mechanism of action of estrogen in non-reproductive vs. reproductive tissues and emphasized the importance of activation of the non-genomic pathway in non-reproductive tissues.

Interdependence of estrogen- and androgen-signaling pathways

Traditionally, it was generally believed that the role of estrogen and testosterone was gender specific. In recent years, it has become clear that the concept that androgens are male hormones and estrogens female hormones is an oversimplification. Studies on estrogen receptor knockout mice have revealed an important role for estrogen in the skeleton, the cardiovascular system, and the reproductive tract of males (94–96). By contrast, studies on 5α-reductase-deficient mice have shown that androgens are important for reproductive function of females (97–99). Although it is clear that the transcriptional effects of estrogen and testosterone are mediated by the estrogen and androgen receptor, respectively, Kousteni et al. (83) have found that the effects of sex steroids on preventing osteoblast apoptosis, which is mediated by the non-genomic actions involving the MAPK-signaling pathway, appear to be gender non-specific. These effects are mediated by the ligand (rather than DNA) binding domain of ER-α, ER-β, or androgen receptor, and can be transmitted with similar efficiency irrespective of whether the ligand is estrogen or an androgen. Further evidence for this molecular crosstalk comes from studies in mouse prostate demonstrating that the testosterone metabolite, 5α-androstane-3β-diol, can bind ER-β and thereby reduce androgen receptor levels (100).

Molecular mechanisms of estrogen effects in skin

Estrogen receptors expression in skin

The presence of ER in skin was first demonstrated by binding studies using radioactive estradiol (101,102). However, the studies used whole skin homogenates and did not distinguish between the different cell components of the skin and between the different receptors. With the use of human fetal skin, it has been demonstrated by reverse transcriptase-polymerase chain reaction (RT-PCR) that ER-α and ER-β mRNA are expressed in human skin during mid-gestation (103). Since the development of ER-α- and ER-β-specific antibodies, very few studies have documented the expression of ERs in human skin, and the results are controversial. Thornton et al. (104) showed a strong ER-β expression in the epidermis, dermal fibroblasts, blood vessels, and hair follicles of male and female adult scalp skin, but no specific staining of ER-α was observed. However, we have recently demonstrated by immunostaining of permeabilized and non- permeabilized keratinocytes isolated from neonatal foreskin that ER-α localizes to the membrane as well as to the nucleus (Fig. 2) (105), the same distribution as reported for ER-α in pituitary tumor cells and in MCF-7 breast cancer cells using the same technique (81–106). Furthermore, as reported here for the first time, both ER-α and ER-β are expressed in human neonatal foreskin. Using an immunohistochemical technique, sections of frozen tissues from neonatal foreskin were stained with primary antibodies: anti-ER-α specific (ER-α D12 1:20; Santa Cruz Biotechnology, Santa Cruz, CA, USA) and anti-ER-β specific (ER-β antibody 3577 1:500; Abcam Inc, Cambridge, MA, USA) followed by fluorescein isothiocyanate- or tetramethylrhodamine isocyanate (TRICT)-conjugated secondary antibody staining. Strong ER-β nuclear staining was observed in all the epidermal layers as well as an ER-β staining of underlying fibroblasts. ER-α nuclear staining was observed in epidermal keratinocytes predominant in the stratum basale and stratum spinosum. The underlying fibroblasts also showed nuclear staining for ER-α (Verdier-Sevrain and Li, unpublished observations). The discrepancies between new and previously published studies may be the consequence of donor age (newborn vs. adult), site (foreskin vs. scalp), or different antibodies.

Estrogen and fibroblast function

It has been shown by RT-PCR that ER-α and ER-β mRNA are expressed in human dermal fibroblasts

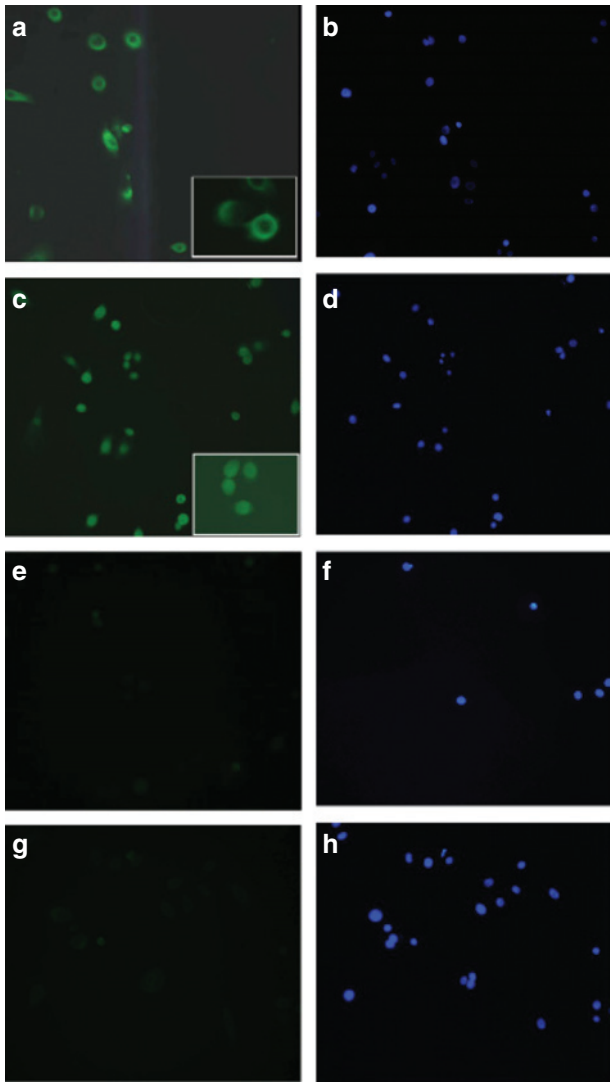

Figure 2. Keratinocytes express membrane associated as well as nuclear ER-α. Keratinocytes were maintained in phenol red containing Epilife medium. Cells on cover slips were fixed with paraformaldehyde/glutaraldehyde that contained no detergent (non-permeabilized cells a, b, e, f) or with the same fixative containing 0.5% NP-40 (permeabilized cells c, d, g, h) and then incubated with ER-α antibody (a, b, c, d) or with diluent alone (e, f, g, h). Nuclei were stained with Hoescht no: 33258 (b, d, f, h) [magnification ×20 (×40, insets)]. (a) ER-α antibody labeling of non-permeabilized cells shows plasma membrane staining best seen at higher magnification (inset). (b) Hoescht nuclear staining of non-permeabilized cells. (c) ER-α antibody labeling of permeabilized cells showing nuclear staining best seen at higher magnification (inset). (d) Hoescht nuclear staining of permeabilized cells. (e and f) Control non-permeabilized cells labeled with the secondary antibody alone (e) or stained with Hoescht nuclear staining (f). (g and h) Control permeabilized cells labeled with the secondary antibody alone (g) or stained with Hoescht nuclear staining (h) (105).

(107) strongly suggesting that estradiol mediates its effects on the dermis through direct regulation of fibroblast function mediated by ERs. However, the precise mechanisms of estrogen-induced increase in collagen content are still poorly known. Regulation

of the levels of transforming growth factor-β (TGF-β), a growth factor known to promote collagen production, seems to play a role. Indeed, Ashcroft et al. (108) showed that estradiol accelerates wound healing by increasing the level of TGF-β1 production by dermal fibroblasts. Furthermore, others report that tamoxifen, an estrogen receptor antagonist, decreases cheloid fibroblast collagen synthesis by decreasing TGF-β production (109). Surazynski et al. (110) studied the effects of estradiol and raloxifene, a selective estrogen receptor modulator (SERM) currently used in the treatment of postmenopausal osteoporosis, on different factors, such as ER expression, prolidase activity, insulin-like growth factor I receptor (IGF-1R), and matrix metalloproteinase (MMP)-9 expression, all influencing collagen biosynthesis in human skin fibroblasts. They show that in human skin fibroblasts raloxifene had stronger positive stimulative effect on collagen synthesis than estradiol. They reported that estradiol and raloxifene increase the expression of both ER mRNA levels in fibroblasts, increase prolidase activity, and increase IGF-1R expression and that raloxifene but not estradiol decreases the expression of MMP-9.

Estrogen and keratinocyte function

Because most studies highlighted the increase in skin thickness and skin collagen content after estrogen therapy, fibroblasts have been considered the main target of estrogen in skin. However, it is known also that epidermis atrophies with age and this epidermal atrophy can be reversed by oral estrogen therapy (111). In 1995, Urano et al. (112) reported that E2 *in vitro* stimulates proliferation and DNA synthesis of human keratinocytes. Recently, two different laboratories (105,113) confirmed the stimulatory effects of E2 on the keratinocytes and analyzed the mechanisms of these effects. Kanda et al. (113) demonstrated that E2 suppresses apoptosis in keratinocytes by promoting Bcl-2 expression (114) and induced the expression of cyclin D2 (113), an important cell-cycle regulatory protein. They showed that E2 mediates its effects by interacting with a cell-surface receptor identified as GPR30, which activates the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)- signaling pathway. In the same time, we (105) demonstrated that E2 stimulates the expression of cyclin D1, another important cell-cycle regulatory protein. We reported that the E2 effects are mediated by membrane ER-α which activates the MAPK pathway. There are some discrepancies in these two reports, and additional studies are necessary to better characterize the molecular mechanisms of E2 effect in the epidermis. Nevertheless, these results emphasize the role of a membrane receptor and the activation of the non-genomic pathway in skin, as already reported in other non-reproductive tissues (93).

Estrogen and melanocyte function

The influence of ovarian hormones and especially estrogens on pigmentation is still poorly understood. The presence of estrogen receptors in melanocytes has been demonstrated by binding studies (115) and recently Sungbin et al., using immunocytochemistry and RT-PCR, reported the presence of ER-α in normal human melanocytes (116). A few studies have investigated the effects of estrogen treatment on tyrosinase activity and have reported a stimulation of this melanogenic enzyme (117,118). By contrast, it has also been demonstrated that melanocytes, at least from the genitalia, are androgen target cells because they express androgen receptors and display high levels of 5α-reductase activity, the enzyme that converts testosterone to its more active form, 5α-DHT (119). It was reported recently that androgens modulate tyrosinase activity via regulation of cAMP, a key regulator of skin pigmentation (120). This emphasizes the importance of both sex hormones for the control of skin pigmentation. Changes in hormonal status occurring in postmenopausal women might affect the function of melanocytes, but the molecular mechanisms underlying these effects are just beginning to be investigated.

Estrogen and hair follicle

A hair follicle consists of epithelial components, which include the inner and outer root sheath and the hair shaft, and mesenchymal components, which include the dermal papilla and connective tissue sheath. Normal development of hair follicles depends on the interactions of the follicular epithelium with the adjacent mesenchymal dermal papilla (121). The hair follicle is a self-renewing system. The bulge region of the outer root sheath contains stem cells for hair follicle keratinocytes that regenerate the follicle during each anagen phase of the hair cycle (122), and dermal papilla cells provide the signal that initiates anagen and instructs the bulge follicular stem cells to divide (123).

The presence of ERs has been documented by immunohistochemical studies in human anagen

hair follicles from both sexes (104–124). In contrast to ER-α, ER-β is widely expressed in the hair follicle with strong staining in dermal papilla cells and in the bulge region of the outer root sheath. These results provide evidence that estradiol mediates its effects on hair follicle through direct regulation of specific cells and suggest an important role of estrogens in regulation of hair growth. However, there is no report on the expression of ER-α and ER-β in human telogen follicles, and the functional role of ER-α/ER-β in the regulation of hair cycle is unknown.

Role of interdependence of estrogen- and androgen-signaling pathways in skin

As already discussed, interdependence of estrogen- and androgen-signaling pathways plays an important role in the mechanism of sex steroids' effect on target tissues.

Because androgen receptors are expressed in skin (125), such interactions between estrogens and androgens may also be important in the control of skin physiology. This is particularly relevant for the hair follicle, which is a well-known androgen target tissue also influenced by estrogen. Recent studies have reported that both androgen receptor and ER-β are expressed in follicular dermal papilla cells (124,125). Further studies are required to determine whether androgen metabolites, acting over ER-β, affect follicular dermal papilla cells, as occurs in mouse prostate.

Conclusion

The skin is an estrogen-responsive tissue and responds to estrogens via specific receptors. We are just beginning to understand the molecular processes involved. Among many questions that need to be addressed are the role of the receptor subtypes ER-α and ER-β, the importance of the non-genomic vs. genomic activities, the interdependence of estrogen- and androgen-signaling pathways. This will lead to a better understanding of the hormonal regulation of skin physiology and skin aging and may provide the basis for development of new hormonal treatment for skin aging. While HRT has been recommended for many years to treat the symptoms of menopause and to prevent postmenopausal osteoporosis, recent outcomes from the Heart and Estrogen/Progestin Replacement Study and Women's Health Initiative (WHI) studies have indicated increased risk of coronary artery disease and breast cancer associated with HRT (126–128). This has led to careful reconsideration of the risks and benefits of systemic HRT. For this reason, HRT cannot be recommended to treat skin aging and topical estrogen cannot be used before conducting clinical studies to find the minimum concentration of estrogen compound that achieves the best local effects without systemic hormonal side effects. Phytoestrogens, non-steroidal plant compounds with estrogen-like biological activity, seem promising alternative for skin aging treatment. In particular, isoflavone-containing cosmetic creams were shown to improve skin dryness and wrinkles (129). However, the precise mechanism of action of phytoestrogens in skin is still unknown, and their possible side effects have not been well investigated.

Currently, intensive research is being conducted on new drugs – SERMs (130). These drugs exert mixed estrogenic and antiestrogenic effects depending on the tissue and cell type. Tamoxifen, the first SERM developed, has antiestrogenic effect on breast tissue but estrogenic effect on bone and is used to treat breast cancer but in the same time prevent postmenopausal osteoporosis. Other SERMs are in development, and one might expect in the future such a drug targeting specifically the skin without systemic side effects.

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