Dermato-Endocrinology 5:2, 264–270; April/May/June 2013; © 2013 Landes Bioscience

Estrogens and aging skin

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Keywords: estrogen, skin, menopause, phytoestrogen, SERMs, aging, wound healing

Estrogen deficiency following menopause results in atrophic skin changes and acceleration of skin aging. Estrogens significantly modulate skin physiology, targeting keratinocytes, fibroblasts, melanocytes, hair follicles and sebaceous glands, and improve angiogenesis, wound healing and immune responses. Estrogen insufficiency decreases defense against oxidative stress; skin becomes thinner with less collagen, decreased elasticity, increased wrinkling, increased dryness and reduced vascularity. Its protective function becomes compromised and aging is associated with impaired wound healing, hair loss, pigmentary changes and skin cancer.

Skin aging can be significantly delayed by the administration of estrogen. This paper reviews estrogen effects on human skin and the mechanisms by which estrogens can alleviate the changes due to aging. The relevance of estrogen replacement, selective estrogen receptor modulators (SERMs) and phytoestrogens as therapies for diminishing skin aging is highlighted. Understanding estrogen signaling in skin will provide a basis for interventions in aging pathologies.

Aging and Estrogen Deficiency

Multiple endocrine changes are associated with aging, but the best example of programmed aging in mammals is demonstrated by aging in the female reproductive system. The menopause is the result of a transition from full ovarian function to a complete lack of ovarian estrogen biosynthesis occurring in women around the age of 50 years old. Since Allen and Doisy first identified estrogen as a hormone in 1923,[1] its importance in female reproductive tissues has been well established. However, in recent years, this time-honored concept of estrogen as a female sex hormone has significantly altered; it is now apparent that estrogens have additional important and diverse functions in a plethora of tissues in both sexes, including the bone, brain, skeletal muscle, adipose tissue, colon, vascular system and skin; the loss of estrogen with aging has detrimental effects on these tissues, resulting in osteoporosis and an increased risk of cardiovascular disease.[2]

Mechanism of Estrogen Action

The principle source of estrogen biosynthesis in females of reproductive age is the ovary. In men, estradiol can be produced in peripheral tissues by the actions of aromatase on androstenedione and testosterone.[3] Humans are unusual in that the adrenal cortex secretes large quantities of a precursor androgen, dehydroepiandrosterone (DHEA); following conversion into active steroids in peripheral tissues it provides the main source of active estrogens in post-menopausal women.[4] Even so, secretion of DHEA reduces with aging, with levels as low 10–20% of the peak concentrations in the elderly, so peripheral estrogen biosynthesis is also significantly reduced.[4] Estrogens can signal in a multifaceted manner involving diverse receptors that modulate genomic or non-genomic pathways, which in turn may have independent, synergistic, or opposing actions. In addition, cell specific co-factors are also required and ligands that display estrogenic activity in some cells, paradoxically exhibit estrogen antagonism in others.[5]

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Submitted: 08/07/12; Revised: 12/13/12; Accepted: 02/04/13
http://dx.doi.org/10.4161/derm.23872

Classical Mechanism of Action: Genomic Signaling

Two related, but distinct, tissue-dependent intracellular estrogen receptors (ERα and ERβ) have been identified as members of the superfamily family of nuclear hormone receptors.[5,6] The ERα and ERβ proteins share approximately 97% homology in the DNA binding domain, with only a few amino acids differing in this region. However, in the ligand binding domain they only share 59% homology, while they share little homology in other domains.[7] With such a difference in the ligand binding domain, it could be anticipated that the receptors would bind estradiol with different affinities; this however is not the case, since 17β-estradiol has a similar affinity for both receptors.

ERα and ERβ are ligand activated nuclear transcription factors that enhance target-gene transcription upon binding to chromatin. Activation of the target gene by 17β-estradiol initiates an increase in the transcriptional activities via interaction with specific DNA palindrome estrogen response elements (ERE), found in the promoter region of estrogen-regulated target genes.[8] The recruitment of a large coactivator complex composed of p160 coactivators including GRIP1 and SRC-1 and the histone acetyltransferases p300/CREB-binding protein and pCAF are also required.[9] While identification of ERE is mediated by the DNA binding domain, the mediation of coactivator recruitment occurs via distinct activation functions (AF) located in the N-terminal domain (AF-1) and the ligand binding domain (AF-2). Coactivators are tissue-specific and ERα and ERβ can have diverse requirements for coactivators in a cell and tissue dependent manner.[10] In addition, estrogen receptors may also interact with other transcription factors bound to related DNA binding sites through protein-protein interactions. One such example is that either ERα or ERβ can augment the transcription of genes

that contain AP-1 sites, the related binding site for the Jun/Fos complex.[11] When ERα and ERβ are co-localized within a cell, they can form both homodimers and heterodimers, although evidence suggests that ERα homodimers and ERα/ERβ heterodimers are formed in preference to ERβ homodimers, therefore the response of the cell to estrogen may be determined by the ratio of ERα:ERβ.[12]

Estrogen Receptor: Non-Genomic Signaling

While the best described mechanism of estrogen signaling is mediated via the nuclear receptor proteins ERα and ERβ, it is now apparent that many cells also express membrane estrogen receptors coupled to cytosolic signal transduction proteins that direct signaling cascades via conventional second messengers including adenylate cyclase, cAMP, phospholipase C, protein kinase C, and the mitogen-activated protein kinase (MAPK) producing rapid responses to estrogen.[13] Although a number of cell-based studies have suggested G-protein-coupled receptors (GPCR), most notably GPR30 act as cell membrane estrogen receptors, there are few in vivo studies that can provide evidence to support this.[14]

On the other hand, the presence of the classical ERα nuclear receptor has frequently been localized at the cell membrane. Membrane-bound classical ERs appear to work in partnership with GPCRs such as GPR30 located in the cell membrane to transmit rapid signals.[15] Verification that classical ERs are trafficked to the cell membrane following palmitoylation in the cytoplasm is now emerging.[16] Palmitoylation of monomeric ER encourages a physical interaction with the caveolin-1 protein required to help transport ER to the caveolae rafts in the cell membrane.[14] Although membrane-bound classical ERs lack the structural signaling domains of tyrosine kinase receptors, there is increasing evidence that they can also transactivate the EGF or IGF-1 receptors to stimulate kinase cascades.[17] For example, if the IGF-1 signaling pathway is blocked, uterine cells are unresponsive to estradiol while in ERα knockout cells, the effect of IGF-1 on proliferation and gene transactivation is lost.[18] Furthermore, the neuroprotective effects of estradiol are lost in the presence of a specific IGF- 1 receptor antagonist, while estrogen receptors are necessary for IGF-1 dependent neuronal differentiation and survival.[19] Complex interactions between estrogen and IGF-1 signaling pathways have also recently been reported in cultured human skin fibroblasts and the human sebocyte cell line.[20] Furthermore, in ovariectomized mice IGF-1 has been shown to improve wound healing, while it has no effect in ERα null mice.[21] The same study, using specific receptor antagonists, demonstrated that while the effects of IGF-1 on re-epithelialisation were mediated via the IGF-1 receptor, the anti inflammatory effects of IGF-1 were mediated via ERα, providing further support for the complexity of estrogen signaling in the skin.

The Menopause and Skin Aging

Following menopause many women detect a swift commencement of skin aging; skin becomes thinner with decreased collagen content, decreased elasticity, increased wrinkling and increased dryness. Many of these effects can be reversed by estrogen replacement which increases epidermal hydration, skin elasticity and skin thickness as well as reducing skin wrinkles and augmenting the content and quality of collagen and the level of vascularisation.[5,6,13] A recent immunohistochemical study has shown that while there is no difference in the expression of ERα and ERβ between male and female human skin, the expression of ERβ is significantly decreased in the epidermis of those above 70 years of age.[22]

Many of the effects of estrogen on aging human skin have been derived by comparing post-menopausal women taking estrogen replacement therapy with women who have not. An increase in epidermal thickness in human female skin following six months of oral estrogen administration has been reported[23] with an increase in keratinocyte volume and more defined rete ridges.[24] A study of elderly males and females has confirmed that administration of topical estrogen increases keratinocyte proliferation and epidermal thickness after only two weeks.[25] In estrogen deficient women skin thickness is reduced by 1.13% and collagen content by 2% per postmenopausal year.[26] Type I and III skin collagen is thought to decrease by as much as 30% in the first five years after menopause,[27,28] which parallels the reduction in bone mass observed in post-menopausal women.[26] This decrease in skin thickness and collagen content in elderly females correlates with the period of estrogen deficiency rather than chronological age.[26-28] A difference in collagen subtypes has also been recognized in post-menopausal women; compared with pre-menopausal women, post-menopausal women demonstrate a decrease in collagen types I and III and a reduction in the type III/type I ratio within the dermis, again correlating with the period of estrogen deficiency rather than chronological age.[28]

A randomized, double-blind, placebo-controlled trial, has demonstrated that one year of oral estrogen therapy can increase dermal thickness by 30% in post-menopausal women,[24] while a similar trial established that six months of treatment with oral estrogen increases skin collagen by 6.49%.[29] Other studies have reported an increase specifically in collagen type III.[30,31] The increase in response to estrogen therapy in skin collagen content appears to be related to the initial collagen content, since in women with low skin collagen content, initially estrogen is therapeutic, but later becomes purely prophylactic, while in women with only mild collagen loss in the early years following menopause, the effect of estrogen is essentially prophylactic.[26] The topical administration of estrogen can also increase skin collagen as measured by increased levels of type I and type III procollagen.[32] However, with topical administration, the effect of estrogen is confined to the area where it was directly applied.[31,32] Topical estradiol applied to the buttock skin of elderly males and females significantly increased type I procollagen in both sexes, although the increase was significantly higher in women.[25] The same study also demonstrated that estradiol increased tropoelastin and fibrillin, which may be associated with an increase in elastic fibers. In addition, estrogen also increased TGF-β and TGF-β type II receptor expression, which may be related to dermal fibroblast proliferation and extracellular matrix (ECM) secretion, while

it downregulated the expression of matrixmetalloprotease-I (MMP-1), which may explain the increased collagen content seen in estrogen treated skin.[25]

Skin wrinkling is synonymous with aging, but may also be a result of environmental and hormonal factors. Wrinkling is caused by decreased skin elasticity due to elastic degeneration and loss of connective tissue.[33] In early postmenopausal women, skin elasticity can decrease by 1.5% per year, in contrast to women administered topical estrogen which thickens elastic fibers, increases the number of fibers and improves their orientation in the papillary dermis.[34] When women who were at least five years post-menopause and had taken oral estrogen continuously, were compared with women who had never had estrogen replacement, the average wrinkle score was significantly lower in the estrogen-treated group, providing further evidence of the long-term benefits of estrogen therapy on detrimental skin changes associated with aging.[35]

Estrogens and Wound Healing

Aging is associated with impaired wound healing which leads to challenging non-healing chronic wounds. The recognition of the importance of estrogen in skin physiology would suggest it may also have an important role in wound healing. A number of studies have provided evidence that estrogens have a role in all phases of wound healing by modifying the inflammatory response, accelerating re-epithelialisation, stimulating granulation tissue formation and regulating proteolysis.[36] Case-cohort studies on venous ulceration and pressure ulcers in elderly women reported that women over the age of 65 years taking estrogen replacement were less likely to develop venous ulceration (age-adjusted relative risk 0.65) or a pressure ulcer (age-adjusted relative risk 0.68) than those who were not.[37]

The inflammatory phase. Estrogen receptors have been identified in human leucocytes, monocytes, macrophages and megakaryocytes and there is evidence to suggest that estrogens can affect the function of inflammatory cells. In human subjects treated with topical estrogen a reduced number of neutrophils were seen at the wound site seven days post-wounding.[38] Furthermore, estrogen altered the expression of neutrophil adhesion molecules and downregulated the expression of L-selectin, thereby reducing the ability of neutrophils to localize to sites of inflammation.[38] Impaired wound healing associated with aging is coupled with excessive neutrophil recruitment and protease production[39] and reduced fibronectin levels.[40] Since estrogen therapy reduces the number of wound neutrophils it follows that indirectly it should increase wound fibronectin levels. Ashcroft and colleagues[38] demonstrated that estrogen therapy was associated with reduced elastase activity and less degradation of fibronectin in human wound tissue. Estrogen has also been shown to downregulate the expression of macrophage migration inhibition factor (MIF),[41] a pro-inflammatory cytokine released by monocytes, T lymphocytes, endothelial cells and keratinocytes.

The proliferative phase. The proliferative phase of wound healing involves re-epithelialisation, angiogenesis, formation of granulation tissue and wound contraction. A comparison of wound healing in pre- and post-menopausal women identified delayed re-epithelialisation in the post-menopausal group, which was reversed in women administered with replacement estrogen.[42] The application of topical estrogen patches immediately prior to, and following wounding, has also been shown to increase the rate of re-epithelialisation in both sexes, coupled with a reduction in wound size.[38]

In the wounds of post-menopausal estrogen-deficient women, reduced collagen deposition was also demonstrated when compared with young women, while in post-menopausal women taking estrogen replacement, wound healing was comparable to that of the younger age group.[42] Furthermore, in elderly males and females treated with topical estrogen prior to wounding, increased collagen levels were demonstrated at day seven post-wounding.[38] Interestingly, females deposited more collagen than their male counterparts.

The dermal fibroblast is the key mesenchymal cell involved in wound healing, expressing both ERα and ERβ.[43] Estrogen stimulates the migration of cultured human dermal fibroblasts derived from scalp,[43] breast,[44] and abdominal skin.[45] Interestingly, increased migration occurred only in response to 17β-estradiol and an ERα agonist, while an ERβ agonist had no effect.[45] The importance of ERα was highlighted further by the observation that migration in the presence of the ERα agonist was higher than that seen with 17β-estradiol alone.[45] Since a significant acceleration of cell migration was seen as early as 4 h, this suggests a non-genomic signaling pathway, perhaps via a cell membrane ERα.

TGF-β1 plays a key role in wound healing and in vivo, TGF-β1 expression is decreased in wounds of elderly females compared with younger counterparts, a reduction reversed by estrogen replacement,[42] suggesting that estrogen may indirectly influence granulation tissue formation by altering cytokine profiles within healing wounds. In vitro studies of human dermal fibroblasts have demonstrated an increase in TGF-β1 secretion in response to estradiol.[44] When the fibroblast monolayers were mechanically wounded in culture, this also stimulated secretion of TGF-β1, but paradoxically, estradiol inhibited the secretion of TGF-β1 in the mechanically wounded dermal fibroblasts.[44]

The remodelling phase. The remodelling phase of wound healing relies on a controlled balance between synthesis and degradation of the ECM, with estrogen thought to influence both. In humans, estrogen is also associated with an overall increase in collagen deposition during the remodelling phase.[38,42] This suggests estrogen may affect the balance between collagen synthesis and degradation and studies have demonstrated that although aging is associated with an increase in MMP expression, specifically MMP-2 and MMP-9, staining for MMP-9 was most obvious in elderly females, suggesting that the reduction in estrogen that occurs postmenopausally may affect proteinase production.[40]

Estrogen and the Hair Cycle

Estrogens significantly inhibit hair growth in a number of mammalian species, but regulation of the hair cycle in humans by estrogens appears more complex.[46] In vivo, estradiol prolongs the

anagen phase of the hair follicle, which is also evident during pregnancy when an increase in the number of hairs in anagen is seen.[47] Postpartum, these additional anagen follicles enter telogen, which causes increased hair loss and a temporary thinning of the hair. Limited trichogram evidence suggests that estrogens decrease the telogen rate and prolong the anagen phase when used to treat female pattern hair loss.[6] More recently it has been demonstrated that female pattern hair loss is linked to polymorphisms of the ERβ gene.[48] Further evidence comes from the use of aromatase inhibitors, which prevent the synthesis of estrogens; in these women a common treatment-related side-effect is scalp hair thinning[6] and a recent study has described a link between the risk of female pattern hair loss and a polymorphism of the gene encoding aromatase.[49] However, the response to estrogens by human hair follicles in vitro appears to show differences in terms of gender and site.[46]

In situ, immunohistochemical studies have shown that in contrast to ERα, ERβ is strongly expressed in human non-balding scalp anagen hair follicles derived from both men and women.[50,51] A more recent study using quantitative real-time RT-PCR has demonstrated that the expression of ERβ transcripts is significantly higher than the expression of ERα transcripts in cultured human dermal papilla, dermal sheath and dermal fibroblasts derived from female scalp.[43]

Estrogens and Skin Pigmentation

In humans, hyperpigmentation has been documented during pregnancy (melasma), in women ingesting oral contraceptives containing estrogens and in female and male infants treated with ointments containing estrogen.[52] Particular regions of the body seem to be affected such as the genitals, abdomen, linea alba, face and mammary areola.[5] These clinical observations suggest that melanocytes can respond to estrogens by increasing their levels of pigmentation. However, the precise effect of estrogens on human melanocyte and melanoma biology remains controversial, and is exacerbated by a significant lack of information on the relative expression of estrogen receptors in both human melanocytes and melanomas.[5]

Tyrosinase is the rate limiting enzyme in melanogenesis, catalyzing the conversion of L-tyrosine to 3,4-dihydroxyindole (DOPA), DOPA to DOPAquinone and subsequently DOPAquinone to 5,6-dihydroxyindole to indole-5,6-quinone, which polymerises to produce melanin.[53] Therefore, tyrosinase activity can be determined by DOPA oxidase activity. Studies using proliferating melanocyte cultures showed that the M-box of *Dopachrome tautomerase* (DCT), a member of the tyrosinase gene family that includes the MITF CATGTG binding motif sequence, overlaps with the ERα binding element.[54] Proliferating melanocytes contained these MITF and ERα complexes, while in senescent cells only ERα complexes were found. These researchers also reported that MITF, together with ERα and the histone acetyltransferase p300, can synergistically induce high levels of *DCT* gene transcription in normal proliferating melanocytes. Collectively, these results suggest a mechanism for estrogens to directly regulate the *DCT* gene, leading to hyperpigmentation as seen in some pigmentation disorders associated with elevated levels of estrogens.

Non-Melanoma Skin Cancer

Interestingly, men exceed women in terms of incidence and mortality for basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), with the incidence of non-melanoma skin cancer 2-fold higher in men compared with women[55] and mortality rates from SCC higher in men than women.[56] Furthermore, of patients with a prior skin cancer, men have a 50% greater risk of developing a new BCC and a 3-fold higher risk of developing a new SCC[57] suggesting that women have some protection.

Aging Skin and Oxidative Stress

One of the hallmarks associated with chronological skin aging is an increase in inflammation. Premature skin aging or photoaging due to UV exposure induces chronic low grade inflammation which damages the skin by increasing the expression of proinflammatory cytokines and MMPs leading to detrimental changes.[58] In normal skin, cellular mitochondrial metabolism produces reactive oxygen species (ROS). The presence of antioxidant enzymes such as superoxide dismutase (SOD) maintains normal levels of ROS homeostasis and minimizes the level of cellular stress. Both UV exposure and inflammation result in elevated ROS and oxidative stress, increasing damage to DNA, proteins and lipids and lead to premature aging.[59]

Estrogens have been demonstrated to have cytoprotective effects in a number of cells and tissues, although their precise mechanism of action is unclear. Friedreich's ataxia is an inherited autosomal recessive condition that results in the functional absence of the protein Frataxin.[60] Since Frataxin is responsible for preventing the formation of ROS, its absence contributes to the development of a wide range of neurological disorders such as Alzheimer, Parkinson and Huntington disease.[61] Dermal fibroblasts derived from the skin of these individuals are extremely sensitive to free radical damage and oxidative stress. A recent study has demonstrated that estrogens can protect against oxidative stress induced in these fibroblasts, but the mechanism appears to be independent of the intracellular receptors ERα, ERβ or GPR30.[60] There is increasing evidence to suggest that the antioxidant property of estrogen is due to the presence of the A-ring phenol which can attenuate ROS created by the Fenton reaction by a cyclic phenol-quinol mechanism.[62] The same group went on to demonstrate that phenolic estrogenic compounds independent of any known ER can prevent oxidative damage to mitochondria in Friedreich's ataxia cultured skin fibroblasts.[63] However, western blot analysis of these fibroblasts only demonstrated small amounts of ERβ, while the presence of ERα was not detected, and there was no comparison to ER levels in normal skin fibroblasts.[63] Normal human skin fibroblasts express mRNA transcripts and protein for both ERα and ERβ in culture, although quantification using real-time RT-PCR demonstrated that the expression of ERβ transcripts was approximately 20-fold higher than expression of ERα transcripts.[43] Exposure of cultured human primary

keratinocytes and dermal fibroblasts to UV has shown that selective ERβ agonists significantly decreased inflammatory markers and MMPs, while an ERα selective agonist had no effect.[64]

Selective Estrogen Receptor Modulators (SERMs)

Although estrogen replacement is effective at managing menopausal symptoms and preventing osteoporosis, the use of estrogens has also been implicated as a risk factor in breast and uterine cancer.[65] The recognition of the unusual properties of the non-steroidal triphenylethylene tamoxifen acing as an estrogen antagonist in some tissues e.g., mammary gland, or an estrogen agonist in others, led to the embodiment of the concept of selective estrogen receptor modulators or SERMs.[66]

The drive to develop a SERM with an ideal agonist/antagonist profile has increased significantly over recent years. A SERM can bind to either ERα or ERβ, causing a conformational change in the receptor which will allow it to recruit essential co-factors, which may be co-activators or co-repressors, depending on either the tissue or the SERM. The complexes may modulate genes by either the classical ERE pathway or via protein-protein interactions.[66] This gives numerous combinations by which SERMS can modulate estrogen receptors in a tissue-specific manner.

However, despite the well documented effects of estrogen on skin physiology and aging, there is still very limited data on the effect of SERMs on the skin.[13] Raloxifene a SERM which is used successfully to prevent and treat postmenopausal osteoporosis, increases collagen biosynthesis in human skin fibroblasts[67] and a recent study has demonstrated that raloxifene has a similar effect to estrogen by increasing skin elasticity in postmenopausal women.[68]

One of the fundamental aspects of cutaneous wound healing is an increase in dermal fibroblast proliferation, and recent studies in our laboratory have shown that monolayers of human dermal fibroblasts derived from peri-menopausal women demonstrate a significantly increased rate of proliferation in response to tamoxifen and raloxifene following mechanical wounding in vitro,[45] supporting the application of SERMs as potential therapeutic agents to improve wound healing in postmenopausal women.

Phytoestrogens

In the early 1920s, Bernard Zondek demonstrated that willow tree flowers mimicked estrogen, confirming the existence of plant estrogens or phytoestrogens. The phytoestrogens daidzein and genistein are naturally occurring isoflavones that are found in numerous edible plants, especially soybeans. The traditional Asian diet is renowned for being rich in soy containing phytoestrogens and epidemiological evidence first suggested the beneficial effects of a diet rich in estrogen-like compounds by comparing the health associated benefits of an Asian diet compared with a Western diet.[69] For example the rate of hip fracture in Asian populations is considerably less than those of whites residing in the United States.[70] Since these polyphenolic compounds can bind both ERα and ERβ and act as both estrogen agonists and antagonists[71] they are considered to be naturally occurring SERMs and are potential contenders to provide a natural form of estrogen replacement in postmenopausal women.

Although in general phytoestrogens bind both ERα and ERβ, the isoflavones genistein and S-equol have a significantly greater affinity for ERβ and therefore can be categorised as ERβ selective agonists.[72] Both have positive effects on human skin; they can reduce UV-induced cell death in cultured keratinocytes, improve skin elasticity, reduce wrinkle depth and increase the production of type 1 procollagen.[73] More recently it has been reported that genistein offers protection against UV induced senescence in cultured human dermal fibroblasts by significantly upregulating intracellular SOD activity in a dose-dependent manner.[74]

Another phytoestrogen, resveratrol found in grapes and red wine, can also activate ERα and ERβ and is a potent antioxidant with strong anti-inflammatory properties.[73] A recent study has demonstrated that resveratrol upregulates mitochondrial SOD in cultured human lung fibroblasts and human neuroblastoma cells.[75] Furthermore, the effect of resveratrol could be abolished by the ER antagonist ICI 182780. The effect of resveratrol on mitochondrial SOD could be replicated with either estradiol or an ERβ agonist, but not an ERα agonist, suggesting that resveratrol upregulates mitochondrial SOD via ERβ.[75]

Conclusions

The menopause causes hypoestrogenism, accelerating age-related deterioration of the skin. Estrogen administration has positive effects on human skin by delaying or preventing skin aging manifestations, but the use of estrogen replacement is a risk factor in breast and uterine cancer. Estrogens have important antioxidant properties, but estrogen signaling is complex and intricate, and estrogens can modulate a plethora of signaling pathways that are often cell or tissue-specific. In addition, there are an increasing number of synthetic compounds (SERMs) or naturally occurring compounds (phytoestrogens) that exhibit agonist or antagonist estrogenic properties, depending on the tissue. These could be ideal candidates to combat skin aging and other detrimental effects of hypoestrogenism, such as osteoporosis if we could exploit the positive effects of estrogen on human health, and avoid the negative aspects of estrogen signaling in tissues such as breast and uterus. Only a better understanding of the mechanisms of estrogen action and the structurally related phytoestrogens will help to identify possible candidates to delay the aging process.

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