Pleiotropic actions of estrogen: a mitochondrial matter

Michael C. Velarde
Buck Institute for Research on Aging, Novato, California
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Estrogen provides many beneficial effects early in life by regulating normal tissue development and several physiological functions. While estrogen replacement therapy (ERT) in women was expected to reduce the health risks associated with the age-related decline in estrogen levels during menopause, ERT also resulted in increased progression to other types of diseases. Hence, distinguishing the signaling pathways that regulate the beneficial and detrimental effects of estrogen is important for developing interventions that selectively harness the hormone’s beneficial effects, while minimizing its side effects. Estrogen can minimize mitochondrial dysfunction, which is thought to contribute to aging phenotypes. Decline in estrogen levels during menopause may lead to progressive mitochondrial dysfunction and may permanently alter cellular response, including that of estrogen (i.e., ERT). This review discusses the interplay between estrogen and mitochondrial function during the aging process and suggests a potential role of mitochondria in influencing the pleiotropic action of estrogen.

mitochondrial dysfunction; aging; estrogen receptor signaling; cellular senescence; reactive oxygen species (ROS)

ESTROGEN AND AGING

Sex differences can affect the function of various tissues. For example, compared with men, women have a longer lifespan, a faster rate of wound healing, and a reduced risk of developing certain diseases, such as dermatitis, liver and bladder cancers, and melanoma (16, 32, 61). However, the mechanisms responsible for sex differences in aging are not well studied and are often neglected. Since estrogen levels are more elevated in women than men, estrogen may play an important role in sex differences during the aging process.

Estrogen is a pleiotropic hormone important for normal tissue development and several physiological functions, such as reproduction, bone development, and skin function (64). In women, decline in the levels of estrogen (particularly of 17β-estradiol) during menopause is associated with numerous age-associated diseases, including hot flashes, bone loss, skin thinning, and delayed wound healing (23, 24, 50). Estrogen replacement therapy (ERT) alleviates some of the consequences of menopause and provides many other beneficial effects, including lowered frequency and severity of hot flashes, decreased bone loss and vertebral fractures, increased bone mass, and reduced colon cancer risk (19). However, ERT also increases the risk of other diseases, such as gallbladder diseases (i.e., cholecystitis and cholelithiasis), and ovarian and endometrial cancer (19). Because the majority of these side effects occur in old age, the positive and negative effects of estrogen may be influenced by age. Indeed, some studies suggest that ERT may be more beneficial and less detrimental in younger women who are within the first few years of their menopause than older women who are several years away from their menopausal transition (19). For example, ERT may reduce colon cancer risk in younger but not older women (12, 33), while it may increase coronary heart disease in older but not younger women (25, 53).

Age-dependent action of estrogen may be involved in an antagonistic pleiotropy phenomenon, wherein the beneficial effects of estrogen early in life is advantageous for survival and procreation of the species, even though estrogen (i.e., ERT) may cause some detrimental effects after the reproductive years (3, 65). Understanding the contribution of the aging process to estrogen action, and vice versa, may help explain the pleiotropic responses of estrogen, providing insights into how to alleviate the detrimental effects of estrogen, while maintaining its beneficial effects.

ESTROGEN ACTION AND MITOCHONDRIAL FUNCTION

Estrogen classically signals through two related but distinct estrogen receptor (ER) isoforms, ERα (also ESR1) and ERβ (also ESR2), which function as either homo- or heterodimers (30, 58). Estrogen-activated ERs bind either to estrogen response elements or to other DNA-binding proteins located at promoters of estrogen-regulated genes (35, 54). This interaction facilitates recruitment of specific coactivators and chromatin remodeling enzymes, capable of influencing the tran-
Estrogen regulates mitochondrial structure, biogenesis, and function in various cell types, including those that have a high energy demand, e.g., brain, heart, and lens (20, 36, 56). Estrogen increases mitochondrial electron transport chain efficiency and prevents mitochondrial dysfunction, e.g., ATP depletion and reduced membrane potential (55, 57). Estrogen regulates mitochondrial function indirectly by modulating expression of nuclear-encoded mitochondrial proteins or by activating cytoplasmic signaling cascades (2). Interestingly, estrogen may also directly regulate mitochondrial function, as ERs have been found to associate with mitochondria in various cell types (10). Knockdown of the ERβ1 isoform, which localizes specifically to mitochondria, eliminates estrogen-dependent protection against peroxide-induced mitochondrial membrane depolarization (21). Expression of a mitochondria-targeted, but not a nuclear-targeted ER, conferred estrogen-dependent inhibition of UV-induced mitochondrial depolarization (48), further supporting the role of estrogen-activated ER in regulating mitochondrial function.

Mitochondria play important roles in several aspects of cellular physiology, including ATP production, calcium homeostasis, metabolism, and apoptosis (52). Mitochondrial dysfunction can disrupt normal cellular function and contribute to aging in many tissues (5, 27, 63). Mitochondrial dysfunction can also promote a permanent cell growth arrest, termed cellular senescence (6, 28, 42–45, 47). While cellular senescence can act as an important tumor suppressor to arrest cells during oncogenic stress (8), it can also negatively impact tissue function and contribute to aging and age-related diseases (1, 7). In fact, ablation of senescent cells can reduce the accelerated aging-related pathologies in a progeroid mouse model (4). The ability of estrogen to preserve mitochondrial function suggests that estrogen can inhibit mitochondrial damage-induced cellular senescence and potentially retard the aging process. Indeed, some reports have already shown that estrogen can prevent senescence in cells, such as endothelial progenitor cells (31) and bone marrow stromal osteoblasts (11).

While the mechanism by which mitochondrial dysfunction promotes cellular senescence is still unclear, it is thought that reactive oxygen species (ROS) generated by mitochondria as byproducts of oxidative phosphorylation can contribute to cellular senescence (39, 46). ROS are continuously detoxified by mitochondrial antioxidant enzymes, but when ROS are excessive, the resulting damaged mitochondria can promote cells to senesce (38–39). Contribution of mitochondrial oxidative damage to cellular senescence has also been observed in vivo. For example, deficiency in superoxide dismutase 2 (Sod2), a mitochondrial localized antioxidant enzyme that converts superoxide to less harmful hydrogen peroxide, promotes mitochondrial dysfunction in mouse skin epidermis, resulting in increased cellular senescence and decreased epidermal thickness (60). Specific sod2 deficiency in mouse connective tissues also contributes to increased cellular senescence and accelerated aging phenotypes (59). Interestingly, estrogen-activated estrogen receptor can increase mitochondrial SOD2 protein activity and reduce mitochondrial oxidative damage (48), further supporting estrogen as a potential suppressor of cellular senescence.

**DYSFUNCTIONAL MITOCHONDRIA ON ESTROGEN ACTION IN SENESCENT CELLS: A HYPOTHESIS**

Aberrant changes in cell physiology during aging can critically affect estrogen action. For example, the benefits of estrogen action in preventing Alzheimer’s disease depend on the initial health status of the individual: estrogen is beneficial if the brain is healthy (i.e., young) at the time of exposure, but it becomes deleterious if the brain is already dysfunctional (i.e., old) during treatment (44). Age-associated accumulation of mitochondrial DNA mutations can significantly alter cellular function (26, 62); hence, mitochondrial integrity may play an important role in regulating estrogen action during aging.

Accumulation of mitochondrial DNA mutations may lead to progressive mitochondrial dysfunction with age (13). Consistently, as mitochondrial dysfunction can promote cellular senescence, senescent cells also accumulate with age (18, 41, 60). Because of the pleiotropic effect of estrogen, it is tempting to speculate that the elevated numbers of senescent cells in older but not younger tissues may alter estrogen response. Accumulation of senescent cells may contribute to the detrimental effects of ERT in postmenopausal women. This hypothesis is supported by data showing that accumulation of senescent cells is associated with.

![Fig. 1. Mitochondrial function influences estrogen action](http://physiolgenomics.physiology.org)
increased tumorigenesis, which is one of the health risks during ERT (17, 37).

Senescent cells distinctly upregulate the expression of several inflammatory cytokines (14, 15). This widely observed phenomenon, termed as the senescence-associated secretory phenotype, is hypothesized to be due to a large-scale chromatin remodeling, which permits the overexpression of inflammation-associated genes in senescent cells (22). Interestingly, several of these genes (e.g., matrix metalloproteinase-3, tissue inhibitor of metalloproteinases 1, interleukin-6, and granulocytic-macrophage colony-stimulating factor) are known to be downregulated by estrogen (9, 34, 49), suggesting that senescent cells may potentially counter normal estrogen response.

Senescent cells also develop distinct senescence-associated heterochromatin foci (SAHF), which comprise a closed chromatin structure containing repressed genes (43). Since classical estrogen action requires binding of activated ER to genomic DNA, SAHFs in senescent cells may restrict activation of certain important estrogen-regulated genes. Interestingly, the mitochondrial localized prohibitin, a known repressor of estrogen receptor, can translocate to the nucleus and associate with nuclear foci of cells following cellular senescence (29, 51), further supporting the idea that senescent cells can contain gene loci refractory to ER action. Hence, senescent cells can potentially hamper expression of certain genes and alter estrogen response in aged tissues.

CONCLUSION

The pleiotropic action of estrogen has been an important subject of research in many aspects of basic and translational biology. Early in life, estrogen provides several beneficial effects, including preserving mitochondrial integrity and maintaining normal physiological function (Fig. 1). However, accumulation of mitochondrial dysfunction during aging leads to increased cellular senescence. In turn, accumulation of senescent cells can alter cellular signaling, such as estrogen response, resulting in increased risk to various diseases (Fig. 1). The interplay between estrogen and mitochondrial function during the aging process may partly explain the pleiotropic action of estrogen. Hence, further investigation in this area may provide insights into how to properly prescribe estrogen regimens in young or older individuals.

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