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Pleiotropic actions of estrogen: a mitochondrial matter

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Velarde MC. Pleiotropic actions of estrogen: a mitochondrial matter. Physiol Genomics 45: 106–109, 2013. First published December 18, 2012; doi:10.1152/physiolgenomics.00155.2012.—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 cholesterolithiasis), 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-
It is thought that senescence in cells, such as endothelial progenitor cells (31), can also promote a permanent cell growth arrest, termed cellular senescence (6, 28, 42–45, 47). While cellular senescence can also promote a permanent cell growth arrest, termed 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 mitochondrial dysfunction (48), further supporting estrogen as a potential repressor of cellular senescence.

Fig. 1. Mitochondrial function influences estrogen action. When cells contain healthy mitochondria early in life, estrogen provides beneficial effects to the cell by preserving mitochondrial integrity and maintaining normal cell signaling (green arrows). When cells contain damaged mitochondria and become senescent during aging, estrogen promotes detrimental effects to the cells by altering estrogen signaling (orange arrow).
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 granulocyte-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 s), 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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