New Insights Into Metabolic Regulation via Bifurcated Function of Estrogen Receptor α

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Estrogen plays multifunctional roles in the regulation of human physiology, including sexual function and reproduction, immunity, neural function, bone metabolism, and energy homeostasis (1,2). Although clinical trials demonstrated the beneficial effect of estrogen supplementation on glucose and lipid metabolism in menopausal women (3,4), hormone replacement therapy to improve metabolism is not practical because of the possible risk for estrogen-dependent malignancies and cardiovascular disease.

Recent reports have indicated that there are at least three functional estrogen receptors: the classical nuclear estrogen receptor α (ERα) and β (ERβ), and the endoplasmic reticulum-localized G protein–coupled receptor GPR30 (5,6). Studies using genetic knockout mice revealed the functional differences of these receptors on the distinct actions of estradiol (E2). Accumulating evidence indicates that ERα plays a predominant role in regulation of glucose and lipid metabolism (2,7–11). For instance, myeloid-specific ERα knockout mice showed obesity and adipose tissue inflammation with insulin resistance (7). Treatment with estrogen failed to improve high-fat diet (HFD)–induced insulin resistance and fatty liver in hepatocyte-specific ERα knockout mice (8). More recently, E2 has emerged as a central regulator of both energy metabolism and physical activity (9–11). Central effects of E2 were sufficient to increase energy expenditure and physical activity, suppress the expression of hepatic gluconeogenic genes, and reduce fat volume in HFD-induced and ovariectomized obese mice (11). Furthermore, mice lacking ERα specifically in the hypothalamic steroidogenic factor 1 neuron showed decreased energy expenditure and abdominal obesity, while pro-opiomelanocortin neuron–specific ERα knockout mice showed hyperphagia (10). Together, the evidence clearly indicates that the beneficial effects of estrogen on maintenance of energy balance are mainly mediated by ERα.

ERα is composed of six functional domains: N-terminal A/B, DNA-binding, hinge region, hormone-binding, and COOH-terminal (12,13). Two transcriptionally important regions, activation function 1 (AF1) and activation function 2 (AF2), are located in N-terminal A/B and hormone-binding domains, respectively (Fig. 1). Although both AFs are important for E2-induced transactivation in ERα, AF2 is indispensable for proper ligand-dependent activation, while AF1 possesses stable transactivation activity that is suppressed by AF2 in the absence of ligand binding (12,13). Although common transcriptional coactivators and corepressors bind to both AF1 and AF2, certain cofactors specifically bind to either AF1 or AF2 for distinct transcriptional regulation. Currently, increasing attention is being paid to the specific roles of these transcriptional cofactors in elucidating the mechanism behind the multifunctional actions of estrogen.

In this issue, Handgraaf et al. (14) identified the functional significance of AF2 domain of ERα on estrogen control of glucose and energy homeostasis in an elegant series of experiments using mice lacking the AF1 or AF2 domain in ERα (*ERαAF-1°* and *ERαAF-2°*, respectively). Like ERα knockout mice ($ER\alpha^{-/-}$), *ERαAF-2°* male and female mice developed accelerated weight gain, massive adiposity, severe insulin resistance, and glucose intolerance. In contrast, *ERαAF-1°* showed similar body weight and metabolic activities to wild-type mice. In addition, the new report examines the impact of E2 supplementation in ovariectomized and HFD-fed mice. Treatment with E2 enhanced energy expenditure and increased whole-body insulin sensitivity equally in wild-type and *ERαAF-1°* mice, whereas these beneficial effects were not observed in $ER\alpha^{-/-}$ and *ERαAF-2°* mice. To explore the mechanism underlying different functions of AFs, Handgraaf et al. investigated the expression of genes related to de novo lipogenesis and lipid metabolism. E2 effectively suppressed most of those genes in wild-type and *ERαAF-1°*, whereas the E2 effects were not evident in $ER\alpha^{-/-}$ and *ERαAF-2°*, both in vivo and in vitro studies. Based on these facts, the new report concludes that the beneficial role of E2 in the regulation of glucose and energy homeostasis is mainly mediated through AF2, but not AF1, of ERα. Interestingly, plasma concentration of E2 was markedly elevated in $ER\alpha^{-/-}$ by a possible feedback mechanism, in contrast to mild elevation in *ERαAF-2°*. Although the current study offers significant progress in our understanding of these mechanisms, additional unknown mechanisms are likely to exist in explaining the entire function of AF1 and AF2 in activation of ERα.

Notably, recent work demonstrated the significance of noncanonical action of estrogen through ERα on the regulation of glucose and energy metabolism (15). This work used knock-in mice expressing mutant ERα with disrupted binding to estrogen response element (ERE). The mutant ERα could transmit signal via an ERE-independent noncanonical pathway. Amelioration of increased body weight, insulin resistance, decreased locomotor activity, and reduced energy expenditure were all observed in these mice. The discrepancy between this evidence and the findings of Handgraaf et al. needs to be resolved. The noncanonical signal is mediated via protein–protein interaction with other transcriptional factors such as activator protein 1,

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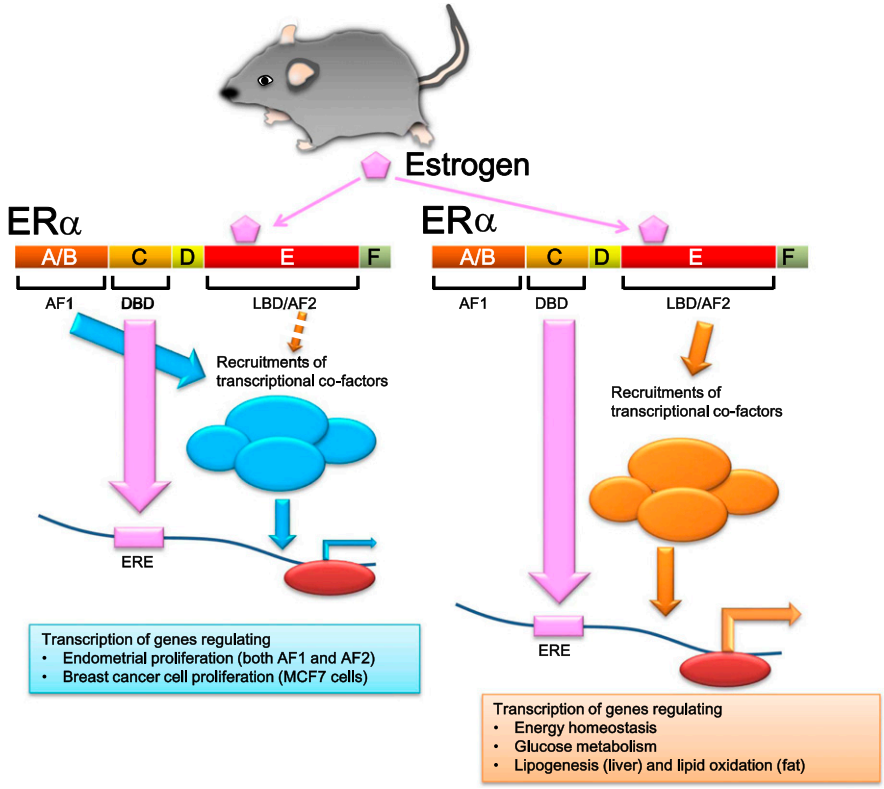

FIG. 1. Bifurcation of genomic functions of estrogen at AF1 and AF2 in ERα. ERα is composed of six functional domains: N-terminal (A/B), DNA-binding (C), hinge region (D), hormone-binding (E), COOH-terminal (F). Estrogen binds to ligand-binding domain (LBD) of ERα and promotes its translocation to the nucleus. Subsequently, the ERα binds to estrogen response elements (ERE) on the promoter region of specific genes via DNA-binding domain (DBD). Both AF1 and AF2 in ERα interact with transcriptional coactivators and/or corepressors and coordinately regulate transcription of genes. Importantly, the metabolic effects of estrogen are mediated through AF2. In contrast, AF1 is responsible for the estrogen-mediated proliferation of endometrial and breast cancer cells.

specificity protein 1, and nuclear factor-κB (15); therefore, one can assume that nonclassical genotropic ERα signaling is also influenced by AF2-mediated regulation of transcriptional cofactors. Further investigation is needed to clarify the role of AFs in the noncanonical action of ERα.

From a clinical point of view, Handgraaf et al. (14) showing the beneficial effect of E2 through AF2 provides a novel therapeutic insight. Although estrogen replacement is effective for glucose and lipid metabolism and obesity in menopausal women, this treatment has been limited by the possible risk of E2-dependent malignancies. In addition, selective estrogen receptor modulators are currently not available for control of energy homeostasis. Since activation of AF1 alone or both AF1 and AF2 is known to be involved in E2-induced endometrial and breast cell proliferation (16,17), specific activation of AF2 of ERα would be a beneficial therapeutic strategy to prevent obesity and improve glucose metabolism without raising the possible risk of E2-dependent malignancies in menopausal women.

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