Estrogen has a number of effects on cardiovascular function and disease. Among its many cardiovascular effects, estrogen modulates vascular function, the inflammatory response, metabolism, insulin sensitivity, cardiac myocyte and stem cell survival, and the development of hypertrophy. Estrogen mediates these effects on the cardiovascular system by activation of estrogen receptors (ER), which can alter gene transcription in the nucleus or acutely activate kinase signaling in the cytosol. ER and their signaling mechanisms are reviewed, along with the cardiovascular effects of estrogen signaling.

How Does Estrogen Alter Cell Function?
The effects of estrogen on cardiovascular function are mediated by ER. There are two nuclear ER, ER-α and ER-β. Estrogen binding to these receptors results in their translocation to the nucleus, where they act as transcription factors leading to altered gene expression. ERα, which is 67 kDa, and ERβ, which is 59 kDa, are highly homologous. The DNA binding domain is conserved (∼97% homologous) between ERα and ERβ, as is the ligand-binding domain (60% homologous). However, ERα and ERβ differ in the amino terminal transcriptional control domain, AF-1, through which regulatory binding partners interact.1 The nuclear ER can alter gene expression by direct binding to DNA (Figure 1A), by binding DNA indirectly via other transcription factors (Figure 1B), or by ligand-independent binding (Figure 1C, D). In addition, the nuclear ER can be localized to the plasma membrane, where it can activate PI3K signaling.

Abstract: Estrogen has pleiotropic effects on the cardiovascular system. The mechanisms by which estrogen confers these pleiotropic effects are undergoing active investigation. Until a decade ago, all estrogen signaling was thought to occur by estrogen binding to nuclear estrogen receptors (estrogen receptor-α and estrogen receptor-β), which bind to DNA and function as ligand-activated transcription factors. Estrogen binding to the receptor alters gene expression, thereby altering cell function. Estrogen also binds to nuclear estrogen receptors that are tethered to the plasma membrane, resulting in acute activation of signaling kinases such as PI3K. An orphan G-protein-coupled receptor, G-protein-coupled receptor 30, can also bind estrogen and activate acute signaling pathways. Thus, estrogen can alter cell function by binding to different estrogen receptors. This article reviews the different estrogen receptors and their signaling mechanisms, discusses mechanisms that regulate estrogen receptor levels and locations, and considers the cardiovascular effects of estrogen signaling. (Circ Res. 2011;109:687-696.)

Key Words: estrogen ■ hormone replacement therapy ■ ischemia-reperfusion ■ nitric oxide
Direct ER Binding to DNA

ERα and ERβ act as ligand-gated receptors to alter gene expression. Estrogen binding to the AF-2 domain of ER results in a conformational change leading to ER dimerization and binding to consensus estrogen response element (ERE) sites on the DNA (Figure 1A). The consensus ERE sequence is 5′ GGTCAnnnTGACC 3′. Coregulators (coactivators and corepressors) are recruited, resulting in an increase or decrease in gene expression. Depending on the coregulators present in the cell, the estrogen–ER complex can have different effects. The coactivators are also commonly shared by different nuclear receptors. The recruitment of coregulators depends in part on the ligand bound, likely attributable to conformational differences with different ligands. For example, tamoxifen is an ER agonist in endometrium because it recruits coactivators, but it is an antagonist in breast because it recruits corepressors.

Indirect ER Binding to DNA

Some genes regulated by ER do not contain an ERE. However, ER can bind to DNA indirectly via transcription factors such as AP1 and Sp1 (Figure 1B). This mechanism is typically referred to as transcriptional cross-talk. Estrogen can lead to both activation and inactivation of AP1-dependent transcription. The DNA binding site of ER was mutated to show that direct ER binding to DNA was not required for estrogen modulation of the AP1 reporter. Mutations in the hinged region of ER demonstrated that this region is important for tethering ER to transcription factors.

Ligand-Independent Binding to DNA

ER can also function in a ligand-independent manner to alter gene transcription (Figure 1C, D). ER can be phosphorylated, allowing it to bind to ERE (Figure 1C) or bind DNA indirectly via transcription factors (Figure 1D) and modulate gene transcription in the absence of ligand binding. Growth factors such as epidermal growth factor can stimulate proliferation, but the stimulatory effect of epidermal growth factor requires the ER. Phosphorylation of ER at specific serine sites is important for ligand-independent activation of transcription. ERα was mutated to decrease estrogen binding to study its ligand-independent effects. Ligand-independent pathways are active in the ER mutant with poor estrogen binding. In addition to phosphorylation of ER, growth factor-dependent phosphorylation of coactivators can also be important to ligand-independent transcription. For example, protein kinase A phosphorylates the coactivator-associated arginine methyltransferase, and phosphorylation of this coactivator is necessary for ligand-independent activation of ERα gene transcription.

Membrane-Initiated Signaling

In addition to the effects of estrogen on gene transcription, estrogen also binds to the nuclear estrogen receptor tethered to the plasma membrane, which has been shown to initiate signaling via PI3K. ERα can undergo palmitoylation at cysteine 447, which leads to its association with caveolin. Estrogen also binds to an orphan G-protein-coupled receptor, GPR30, which can activate rapid kinase signaling pathways such as PI3K and MAPK. Activation of GPR30 also has been reported to reduce ischemia-reperfusion injury and to attenuate cardiac remodeling in salt-sensitive mRen2.Lewis rats. An estrogen-dendrimer conjugate, which is excluded from the nucleus, was used to show that extracellular estrogen can stimulate endothelial cell proliferation and migration via a Gai and endothelial nitric oxide synthase (eNOS)-dependent mechanism.

Mitochondrial Localized ERβ

ERβ has been reported to be localized in the mitochondria, where it is proposed to modulate mitochondrial DNA transcription, although the mass spectrometry identification has been questioned. It has been suggested that mitochondrial ERβ can regulate mitochondrial genes via its association with mitochondrial DNA or mitochondrial transcription factors, or both. Knockdown of ERβ is associated with a lower mitochondrial membrane potential and increased resistance to hydrogen peroxide-mediated decrease in membrane potential.

In summary, the multiple layers of estrogen signaling allow for synergism between the nuclear signaling that alters gene transcription and the ER activation of kinase signaling (Figure 2A). The ability of ER to alter protein expression and alter kinase signaling allows multiple levels of control. For example, in the cardiovascular system, estrogen upregulates eNOS and also acutely activates PI3K signaling, leading to phosphorylation and activation of eNOS. Thus, estrogen can increase nitric oxide.
(NO) signaling in target tissue by increasing the level of eNOS and increasing the activity of eNOS via phosphorylation.

**ERα and ERβ Differentially Regulate Gene Expression**

ERα and ERβ regulate distinct genes in a time- and tissue dependent-manner. These differences are attributed to differences in coactivators and corepressors in different tissue and different levels of ERs relative to ERβ.

Within the same tissue, ERα and ERβ can differentially regulate gene expression. In vascular smooth muscle cells, inducible nitric oxide synthase expression is enhanced by ERβ and repressed by ERα. ERα and ERβ regulate different genes in mouse aorta. ER subtype regulation of gene transcription in mouse aorta in wild-type, ERα knockout, and ERβ knockout ovariectomized (OVX) mice treated with estrogen for 1 week was determined using gene array. ERα was found to primarily upregulate gene expression, whereas ERβ downregulated gene expression; 90% of the genes showing an estrogen mediated decrease were ERβ-dependent. ERβ decreased expression of genes encoding the electron transport complexes. In contrast, electron transport chain expression was reduced in platelets from ERβKO, suggesting that ERβ increases expression of the electron transport chain. This difference could be attributable to a differential regulation in platelets versus aorta or other differences in the model. In contrast to the study with aorta, a gene array study comparing gene expression in mouse hearts from OVX female mice that were perfused for 2 hours with either vehicle or the ERβ selective agonist 2,3-bis(4-hydroxyphenyl)-propionitrile showed that 122 genes were upregulated by ERβ and only 23 genes were downregulated. Gene ontology analysis showed that DNP downregulated contractile protein genes and upregulated immune/chemokine genes and genes involved in regulating cell death. Whether the difference between these studies is attributable to a difference in tissue (aorta vs heart) or to the difference in model (mice null for ERα and ERβ vs treatment with an ERβ agonist) requires further study. There could also be a time-dependent difference in gene expression (2 hours vs 1 week). A number of studies have shown that estrogen...
regulates genes in a time-dependent manner. In vascular tissue, estrogen recruits in a temporal manner specific transcription factors that propagate distinct estrogen signaling. Clearly, additional studies are needed to better-define the role of different ER receptors in regulating gene expression in the cardiovascular system. These ERα-mediated versus ERβ-mediated differences in gene regulation are likely attributable to differential recruitment of corepressors and coactivators.

Several studies have used gene array to examine ER-β-regulated genes. However, different genes are found to be regulated in the different studies. Although a number of genes appear to be regulated by estrogen, because of the limited number of studies and the different conditions and models used in the studies it is not possible to make generalizations about pathways at this time. Other studies have used a candidate gene approach and have identified a number of genes regulated (directly or indirectly) by estrogen, including, peroxisomal proliferator γ-1α,29 connexin 43,30,31 adenine nucleotide transporter 4,32 heat shock proteins,33 mitochondrial complex IV,34 glucose transporter 4,35 and an inhibitor of calcineurin, modulation calcineurin inhibitor protein-1.36 Many of these proteins are involved in cardioprotection. There are also data suggesting male–female differences or estrogen-mediated differences at the protein level.

What Regulates ER Levels?
Because ERα and ERβ differentially regulate gene expression, differences in the expression or activity of ERα and ERβ could have profound effects on gene expression. As discussed, some genes are upregulated by ERα, but others are unaffected or downregulated by ERβ and vice versa. Thus, by altering the relative expression or activity of ERα versus ERβ, one could alter gene expression in the cell and ultimately the phenotype of the cell. GPR30 or plasma membrane-localized ER could also alter gene expression by phosphorylation of the ER receptor, leading to ligand-independent activity. GPR30 activation also has been reported to enhance levels of an ERα36, a variant of ERα.40

ERα and ERβ show different patterns of expression in different cell types. In cardiac myocytes, ERβ is expressed similarly in males and females, but ERα expression is influenced by gender. Long-term estrogen treatment has been reported to increase ERα and decrease ERβ expression in the vasculature. Differences in ER levels are reported in males and females and in premenopausal and postmenopausal women. ERα expression in vascular endothelial cells in premenopausal women is 30% lower during the early follicular phase compared to the late follicular phase. Furthermore, postmenopausal women had ERα levels that were 33% lower than in the late follicular phase. What can account for these differences in ER levels? A number of factors regulate the expression of ERα. Estrogen can positively and negatively regulate ER levels. Other hormones such as progesterone and vitamin D have been reported to negatively regulate ER levels. The effect of estrogen on ER levels is complex. There is an ER response element in many ER promoter regions, and estrogen in many cell types leads to an increase in ER mRNA. However, estrogen binding to the ER also stimulates ubiquitination and proteasome degradation of ER. An interesting mechanism to regulate ERα has been proposed in which a splice variant for ERβ (ERβ2) that binds poorly to estrogen results in degradation of ERα. Myocyte enhancer factor 2 and class II histone deacetylase also regulate ERα expression. Class II histone deacetylase repress ERα via a myocyte enhancer factor 2 response element. The expression of ER levels also changes with cardiovascular disease. Methylation of the promoter of ER reduces ER expression.

In summary, ER levels are regulated by estrogen and hormones. Changes in the level or activity of different ERs also occur with age and disease, and such changes would have profound effects on gene expression in the cell (Figure 3). Future studies are needed to better-define changes in expression and localization of ER with age, sex, and disease in the cardiovascular system.

**Posttranslational Modifications of ER**
As discussed, the activity of the ER can be modulated by posttranslational modifications. Phosphorylation of ER can
result in ligand-independent modulation of gene transcription. The ER is phosphorylated on a number of sites.54 ERK1/2-dependent phosphorylation of ERα on serines 118, 104, and 10 are important for ligand-independent activation.8 The precise role of each phosphorylation site of ER is not known, but at least some have important functional consequences. For example, phosphorylation of ERα on serine 118 is important for tamoxifen inhibition of gene expression in breast cancer.55

The ER can also be S-nitrosylated, which inhibits ER binding to selective EREs.56 It has been proposed that S-nitrosylation of ER could shift the signaling from the nucleus to nongenomic signaling mechanisms. Because ER activation can also lead to an increase in NOS and an increase in activity of NOS via acute kinase signaling mechanisms, the S-nitrosylation of ER could serve as a negative feedback regulator.

ERs can also be modified by acetylation. Acetylation increases the transcriptional activity of ERα.57,58 BRCA1, the breast cancer susceptibility gene, decreases acetylation of ERα, which would reduce ERα transcriptional activity. The mechanism by which BRCA1 decreases acetylation of ERα is still undergoing investigation,59 but it has been suggested that BRCA1 can increase mono-ubiquitination on the same lysines that are targets for acetylation. Thus BRCA1-mediated ubiquitination of ERα would reduce its acetylation and transcriptional activity. The promoter of ER can also be methylated, which decreases ER levels and inactivates ER transcriptional activity.53

As summarized in Figure 3, in addition to regulation by estrogen and other hormones, ER levels and activity also can be regulated by posttranslational modifications. Some modifications such as acetylation increase transcriptional activation, whereas other modifications, such as methylation, decrease ER activity. In addition, posttranslational modifications can compete for the same site. The diversity of mechanisms regulating ER levels and activity needs to be considered in evaluating the effects of estrogen on the cardiovascular system.

**Effects of Estrogen on the Cardiovascular System**

Estrogen has many important effects on the cardiovascular system. Estrogen can impact cardiovascular health and disease by direct effects on the vascular cells or cardiomyocytes or indirectly by systemic effects. A list of some of the important direct and indirect effects of estrogen on the cardiovascular system is provided in Table. Many of the effects listed in Table are complex diseases or processes, and estrogen modulation of these diseases and processes is multifactorial. Estrogen can alter expression or activity of ion channels, contractile proteins, and reactive oxygen species (ROS) production and these effects are likely involved in the regulation of complex diseases. Estrogen has many pleiotropic effects and Table is not comprehensive. A brief survey of the effects of estrogen on cardiac physiology is included. The effects of estrogen on vascular injury, hypertrophy, and ischemia-reperfusion are discussed in more detail.

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**Estrogen Effects on Cardiac Physiology**

Estrogen regulates a large and expanding number of physiological processes, as illustrated in Table. This section is not intended to be a complete discussion of physiological effects of estrogen, but instead it focuses on a few effects of estrogen that are particularly important to the cardiovascular system.

Estrogen can regulate the level and activity of ion channels and can modulate cardiac repolarization. There are male–female differences in calcium and potassium channels and these differences are attributable, at least in part, to estrogen. The mRNA levels of potassium channel components, Kv4.3 and Kv1.5, are decreased with estrogen.60 In another study, estrogen was found to alter the human ether-a-go-go–related channel, which could contribute to the increase in arrhythmias associated with QT prolongation that occur more frequently in women.61 Estrogen can upregulate the Na–Ca exchanger62 and downregulate the L-type Ca channel.63 A recent study found no sex difference in myofilament calcium sensitivity, but they did find a difference in contractile reserve.64 Sex differences in sarcoplasmic reticulum calcium also have been reported.65,66 Estrogen modulation of cardiac ion channels also can occur by nongenomic mechanisms.67 These data illustrate that estrogen can alter ion channels and transporters that can alter cardiac contractility, contractile reserve, repolarization, and susceptibility to arrhythmias.

Several studies have suggested that female mitochondria generate less ROS.39,68–71 Female mitochondria exhibit increased phosphorylation of mitochondrial α-ketoglutarate dehydrogenase, which leads to less ROS generation by this enzyme under conditions of increased NADH.70 How much the effects of estrogen on mitochondrial function are mediated by nuclear ER versus acute signaling pathways versus mitochondrial localized ER will require further study. ROS at low levels is a signaling messenger, whereas at high levels it contributes to cardiovascular disease. Estrogen-mediated differences in ROS production therefore could account for some of the male–female differences in cardiovascular function and disease.

**Estrogen and Vascular Injury and Atherosclerosis**

It is well-established that estrogen improves vascular function and reduces atherosclerosis. This topic has been reviewed in
Estrogen and Cardiac Hypertrophy

There are many studies showing that estrogen can slow the development of cardiac hypertrophy. OVX female C57B6 mice receiving estrogen via minipumps exhibited less cardiac hypertrophy after transaortic constriction compared to mice receiving vehicle. Consistent with this finding, females had less cardiac hypertrophy than males at 2 weeks after transaortic constriction in C57B6 mice. Furthermore, the reduced cardiac hypertrophy observed in intact females compared to males was lost in female mice lacking ERβ, suggesting a role for ERβ in the reduction in hypertrophy. Wild-type OVX female mice and mice lacking ERα showed less cardiac hypertrophy when treated with estrogen than with vehicle; however, mice lacking ERβ treated with estrogen did not show a reduction in cardiac hypertrophy. Taken together, these data suggest a role for ERβ in reducing hypertrophy in females. Estrogen also can lead to a more favorable myocardial remodeling in females.

The details of the mechanism by which estrogen reduced cardiac hypertrophy are still undergoing investigation. OVX females treated with estrogen had less cardiac hypertrophy and they exhibited a concomitant decrease in calcineurin A. Furthermore, the inhibitory effects of estrogen were lost in mice lacking calcineurin A, suggesting that the beneficial effects of estrogen in limiting cardiac hypertrophy is attributable to estrogen-mediated degradation of calcineurin A. It is likely that estrogen alters the expression of additional genes that are important in the response to cardiac hypertrophy.

Estrogen Signaling and Cardioprotection

Acute in vivo administration of estrogen just before ischemia can reduce infarct size. Several groups have shown that intravenous estrogen administration before coronary artery ligation decreases infarct size in rabbits. Estrogen treatment of OVX rabbits decreased infarct size compared to vehicle treatment in rabbits fed a normal and a cholesterol-enriched diet. Treatment of male rats with estrogen for 2 weeks also reduced infarct size. Estradiol also improved contractile function in rat hearts after ischemia and reperfusion. In addition to studies, primarily in rabbits, showing that addition of estrogen can reduce infarct size, a number of studies report reduced infarct size in females compared to males after ischemia and reperfusion.

The mechanism by which estrogen reduces ischemia-reperfusion injury is still undergoing investigation. There are data suggesting a role for signaling via ERβ and ERα, although the results are mixed. ERα is important in reducing endothelial dysfunction after ischemia and reperfusion. The overall protection afforded by estrogen is likely mediated by effects on both myocytes and endothelial cells, and possibly other tissues such as inflammatory cells and stem cells. Estrogen promotes stem cell survival and plays an important role in cardiac repair by bone marrow-derived endothelial progenitor cells after infarction. Estrogen increases survival of cardiomyocytes after myocardial infarction, and females have increased activity of the antiapoptotic kinase Akt, which may contribute to the protection observed in females. The inflammatory response and inflammatory cytokines are also regulated by estrogen, and this could influence the ischemia-reperfusion injury and remodeling. There is a significant increase in activation of inflammatory signaling in mice lacking ERβ. These data are consistent with the studies showing that an ERβ agonist decreased levels of inflammatory cytokines. Thus, estrogen has beneficial effects on the vascular cells, cardiomyocytes, stem cells, and inflammatory cells, and all of these effects are likely to contribute to the reduced ischemia-reperfusion injury observed in females.

Although there is some disagreement regarding the ER involved, estrogen has been reported to upregulate nitric oxide synthase, which appears to be important in protection observed in females. A role for S-nitrosylation of several proteins has been suggested to play a role in the protection observed in females. There are also data suggesting an important role for estrogen activation of kinase signaling pathways such as PI3K. A role for GPR30 in activation of these signaling mechanisms has also been suggested. It is likely that estrogen-mediated protection involves upregulation of important target genes as well as acute activation of kinase signaling pathways (Figure 2A). It is also likely that these pathways synergize to enhance cardioprotection. The observation that acute addition of estrogen just before ischemia reduces infarct size suggests that acute signaling pathways play an important role in protection. It is possible that different estrogen receptors are important for the chronic versus the acute protection observed with estrogen. This would account for some of the discrepancies in the literature.

Although premenopausal women have reduced incidence of cardiovascular disease, there are data suggesting that women who have angioplasty have worse outcomes than men. The reasons for this difference, which are discussed in detail elsewhere, include technical issues relating to smaller vessel size in females and increased comorbidities in premenopausal females who have cardiovascular disease. The number of premenopausal women who have cardiovascular disease is small and it has been proposed that they may have more underlying risk factors. It has also been suggested that although estrogen might reduce the risk of cardiovascular disease, primarily by improving lipid profile or by vascular effects, estrogen may increase the injury resulting from ischemia, either by increased cell death pathways or by...
adverse remodeling. As mentioned previously, acute administration of estrogen in animal models reduces cell death, so this explanation seems less likely. However, it is likely that the effects of estrogen signaling have both beneficial and detrimental effects on ischemia-reperfusion injury, and it is important to better-understand how estrogen alters cell death in this context.

Why Does Hormone Replacement Therapy Fail to Protect?
Premenopausal women have reduced cardiovascular disease and the incidence of cardiovascular disease increases after menopause. As discussed, estrogen has a number of beneficial effects on the cardiovascular system. The beneficial effects of estrogen in the cardiovascular system and reduced cardiovascular disease in premenopausal females led to the hypothesis that estrogen is cardioprotective and formed the basis for the use of hormone replacement therapy (HRT) to reduce cardiovascular disease. It was therefore surprising when several large prospective studies, the Women’s Health Initiative (WHI), and the Heart and Estrogen/Progesterin Replacement study (HERS) found that HRT was not beneficial. Interestingly, in the WHI and HERS trials, HRT resulted in an improvement in lipid profile and a reduction in type 2 diabetes, but despite these beneficial effects HRT did not improve cardiovascular outcomes.

When WHI and HERS trial data were initially released, several proposals were put forth to explain possible reasons why estrogen did not protect in postmenopausal women. As discussed, estrogen has a number of beneficial effects on the cardiovascular system and reduced cardiovascular disease in premenopausal females led to the hypothesis that estrogen is cardioprotective and formed the basis for the use of hormone replacement therapy (HRT) to reduce cardiovascular disease. It was therefore surprising when several large prospective studies, the Women’s Health Initiative (WHI), and the Heart and Estrogen/Progesterin Replacement study (HERS) found that HRT was not beneficial. Interestingly, in the WHI and HERS trials, HRT resulted in an improvement in lipid profile and a reduction in type 2 diabetes, but despite these beneficial effects HRT did not improve cardiovascular outcomes.

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Unresolved Questions and Future Directions
Estrogen can signal by at least three different receptors. These receptors can differentially regulate transcription; therefore, depending on the relative levels of receptors, estrogen can increase, decrease, or have no effect on transcription. Nuclear ER signaling also depends on coregulators, thus altering coregulator levels or posttranslational modification of ER or the coregulators would lead to different responses to estrogen. Differential posttranslational modifications of ERα relative to ERβ could alter the response of the cell to estrogen. ER and GPR30 also can acutely activate PI3K signaling. Based on the complexity of estrogen signaling, it is not surprising that estrogen could have different effects as a function of age and disease, which could be important in the lack of protection with HRT in postmenopausal women.

What are the key unresolved questions regarding ER signaling in the cardiovascular system? We need to know the levels of posttranslational modification of ERα, ERβ, and GPR30 in cardiovascular targets as a function of age, sex, and disease. Additional information regarding the genes in the cardiovascular system that are regulated by ERα, ERβ, and GPR30 and how they change with age and disease would be useful. The mechanisms regulating the localization of the different estrogen receptors and how this affects estrogen signaling is another area for future studies. We need to understand how estrogen regulates cardiovascular function in young healthy women before we can understand why estrogen is not beneficial in aging postmenopausal women.

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