Mechanisms of estrogentic vascular protection

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CARDIOVASCULAR DISEASE is a leading cause of death, the rate of which is greater in men compared with age-matched premenopausal women (1). However, the long-standing hypothesis that estrogen may contribute to this sex-based difference in disease presentation by providing “vascular protection” has recently come under fire. The controversy that estrogen protects against cardiovascular disease arose because results of randomized clinical trials conducted in postmenopausal women using conjugated equine estrogen in combination with medroxyprogesterone acetate for secondary (Heart and Estrogen/progestin Replacement Study, Ref. 14) and primary (Women’s Health Initiative, Ref. 27) prevention failed to show reductions in myocardial infarction and stroke as was predicted based on observational studies of newly menopausal women using estrogen products to relieve symptoms of menopause (2, 4, 6, 11, 18). Explanations of why these differences exist between epidemiologic studies and randomized trials need to be explored mechanistically, including the timing for initiation of estrogen intervention and the type and mode of hormonal treatment used (12), as the majority of evidence provided from the basic science literature indicates that estrogen treatments initiated shortly after ovariectomy of experimental animals reduces vascular response to injury, i.e., provides vascular protection (5). Such protection is likely to occur in males as well as females, as in humans genetic variance in one estrogen receptor (ER), ER-α, is associated with increased atherosclerosis and adverse outcomes in men (23, 24).

Receptors for estrogen have been identified in all components of the vascular wall (endothelium, smooth muscle, adventitial cells). In endothelial cells, several mechanisms are identified by which estrogen, through ligation of its receptor or independent of its receptor, modulate gene transcription, mRNA stability, translation, and posttranslational protein function (for review, see Ref. 21). However, less is known about estrogentic regulation in vascular smooth muscle cells. The paper by Kappert et al. in this issue (16a) adds important information to fill this gap in our knowledge by providing evidence that estrogen and its metabolite methoxyestradiol reduce PDGF receptor (PDGFR)-activated migration and proliferation of cultured aortic smooth muscle cells derived from male rats by inhibiting the downstream signaling activity of rac-1 (Fig. 1). This inhibition is signaled through ERs without affecting PDGFR expression/phosphorylation or consecutive binding of receptor-associated Src homology region 2-containing signaling molecules such as Src homology region 2-containing phosphatase-2, PLC-γ, phosphatidylinositol 3-kinase, RasGAP, and p85. Because proliferation and migration of vascular smooth muscle cells are two processes needed for development of myointimal thickening after vascular injury, identification of cellular processes that limit these processes such as inhibition of Rac1GTPase provides information about how estrogen could limit vascular disease and potential target molecules for new therapeutic interventions.

PDGFR is a tyrosine kinase that in porcine aortic smooth muscle cells induces migration and proliferation but requires phosphorylation and activation of p38 and p42/44 MAPKs. These effects were inhibited by pretreatment with estrogen (17β-estradiol) through ER-β (10). In mouse aortic smooth muscle cells, estrogen reduced the growth by downregulation of PDGFR and limited activation of ERK (9). Growth factors activate ER-α-mediated gene expression in vascular cells through the AF-1 domain of ER-α but not by activation of the MAPK pathway (17). Therefore, the results of the Kappert study (16a) identify an important, yet perhaps redundant, pathway by which estrogen modulates PDGF-activated cell processes.

rac-1 is a small (21 kDa) member of the Rho family of proteins/GTPase. Estrogen downregulates rac-1 mRNA, protein, and activity in cells derived from female animals including that required for angiotensin II-induced NADPH oxidase activity and reactive oxygen production, ovariectomy-induced increases in expression in smooth muscle of spontaneously hypertensive rats, and expression in mononuclear cells derived from women with ovarian hyperstimulation (19). Because estrogen treatment affected the rac-1 pathway in cells derived from male animals, the study provides important insights into how estrogen affects vascular function in males as well as females (25).

Another exciting observation from the study of Kappert et al. (16a) is that the estrogen metabolite methoxyestradiol was also efficacious in inhibiting rac-1. This observation confirms that metabolites of estrogen also have protective activities and suggests that metabolism of 17β-estradiol within vascular tissue activates molecules that bind ERs, perhaps modulating the threshold, duration, and amplitude of the estrogen signal (8,

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