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EDITORIAL COMMENT

On Male-Specific Estrogen Action

Good for the Gander?*

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In recent years, much attention and controversy have surrounded the question of estrogen's role in heart disease prevention and/or progression in women. It is clear that cardiovascular risk increases as estrogen levels decrease in women. Conversely, in men there is an inverse relationship between androgen levels, which decrease with age, and the risk of cardiovascular disease (CVD). Whereas some attribute the increased risk in men and women to aging coincident with decreasing sex steroid levels, there is convincing evidence from animal and human studies that both androgens and estrogens affect the cardiovascular system and blood lipid profiles that contribute to the risk of CVD. Sex differences in pathology that may reflect differential sex steroid action include the fact that the incidence and severity of acute myocarditis, myocardial hypertrophy, and heart failure are higher in men (1). As the complexity of relationships between sex, sex steroid hormones, and CVD becomes increasingly apparent, there is a need for translational approaches to the role of androgens and estrogens in disease pathology. Surprising results from just such an approach are presented in the report from Kararigas et al. (2) in this issue of the *Journal*.

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Hypothesizing that estrogen-mediated gene regulation underlies male-specific impairment of contractile function in cardiomyocytes, the investigators exposed isolated heart tissue from men and women to estradiol and performed microarray gene analysis. Among the probe sets tested, 41 were identified as being differentially regulated by estradiol in cardiac tissue from men compared with women. Of these, the authors further investigated myosin regulatory light chain interacting protein (MYLIP), which was induced in heart tissue of men only. Following estrogen treatment of mice, Mylip RNA increased in isolated cardiomyocytes only from males, and Mylip protein increased only in male heart tissue. Concomitant with the male-specific induction of cardiac Mylip protein, myosin regulatory light chain (Mrlc) protein, a protein involved in contractility, decreased only in male heart tissue. Furthermore, Mylip–Mrlc interaction increased in estrogen-treated male hearts as did ubiquitination of Mrlc. Estrogen treatment of isolated cardiomyocytes in vitro led to impaired contractile function in male, but not female, cardiomyocytes. Thus, in cardiomyocytes, a novel, male-specific regulatory effect of estrogen is conserved between humans and mice, and results in impairment of contractility only in male cardiomyocytes.

Dozens of genes respond acutely to sex steroids in a sexually dimorphic manner in that they are up- or down-regulated by androgens to a greater extent in males and by estrogens to a greater extent in females (3). Furthermore, there are several examples of divergent responses to sex steroids at tissue and cellular levels that are exclusive to males or females. For example, in a previous study, Kararigas et al. (4) found that estrogen up-regulated gene and protein expression of the progesterone receptor in cultured human cardiac tissue from females but not males. In human macrophages, estrogen- and progesterone-mediated inhibition of cholesterol esterification and, by extension, foam cell formation, occurs only in female-derived macrophages (4). Conversely, androgens enhance cholesterol esterification only in male-derived macrophages (4). However, in the current report on Mylip regulation, we have the first seemingly counterintuitive example of a male-specific gene response to estrogen. Because most investigations of sex steroid responses in humans and experimental animals have focused on female responses to estrogens and male responses to androgens, it now appears that many important responses in the "opposite sex" may have gone undetected. Therefore, investigators must broaden their approach to questions of sex steroids and sexually dimorphic phenomena.

The classical pathway for estrogen-mediated gene expression occurs through ligand interaction with estrogen receptors α and β (ESR1 and ESR2), and these receptors can be differentially expressed in a cell-specific manner. In addition, estrogen-receptor complexes recruit coactivator and corepressor proteins in a receptor- and/or cell-specific manner. Several genes relevant to cardiovascular pathology exhibit differential responses to ESR1 and ESR2. For example, differential expression of ESR1 and ESR2 in smooth muscle cells from different vascular beds most likely explains the observed decrease (ESR1-mediated) and increase (ESR2-mediated) in inducible nitric oxide synthase (iNOS) in these cells (5). In endothelial cells, plasminogen activator inhibitor (PAI)-1 is differentially regulated by ESR1 (which activates) and ESR2 (which inhibits), although the 2 receptors bind an estrogen response element in the PAI-1 promoter region to the same extent (6). Differ-

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ential recruitment of transcriptional cofactors may account for this divergent influence of the 2 receptors on PAI-1 induction. Because expression profiling did not reveal significant differences in estrogen receptor expression between cardiac tissues from males and females, Kararigas and coworkers suggest that the sex-specific regulation of Mylip gene expression results from sex-dependent differential recruitment of transcriptional cofactors by the estrogen-receptor complex. Confirmation of this hypothesis would reveal a novel and exciting avenue of investigation in the study of sexually dimorphic gene expression.

Finally, the authors demonstrate that expression levels of MYLIP are higher in the left ventricles of men older than 50 years compared with those of men younger than 40 years. They postulate that estrogen levels increase as men age and are responsible for this age-related increase in Mylip expression. However, in a large longitudinal study, Ferrini and Barrett-Connor found a significant age-dependent decrease in bioavailable estradiol levels in men (7). What is more important, and supported by the Ferrini and Barrett-Connor (8) study, is the highly significant increase in estradiol levels associated with obesity. This increase results from aromatase conversion of androgen to estrogen in adipose tissue. This adipose tissue–dependent increase in estradiol synthesis in men is predicted to up-regulate Mylip expression and may account, in part, for the increased risk of cardiovascular disease associated with obesity and with the increase in cardiovascular events observed in a study of high-dose diethylstilbestrol (DES) treatment of men with prostate cancer (8). Whereas the authors of the current report suggest that Mylip may represent an effective therapeutic target for cardiovascular prevention in elderly men, the accumulating evidence of negative responses to estrogen in older men suggests that the use of aromatase inhibitors may be a more efficacious pharmacological approach. Until now, the potentially important cardiovascular influences of endogenous estrogens in men and endogenous androgens in women have received little attention Clearly, the surprising finding of a gene regulated by estrogen only in male hearts opens the door to a provocative area of research, emphasizes the importance of endogenous estrogen pathophysiological action in men, and reveals novel therapeutic targets for cardiac dysfunction.

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