EDITORIAL

Endometrial Responsiveness to Steroid Hormones: A Moving Target

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The uterine response to estrogen depends on specific estrogen-receptor proteins, as noted independently by Jensen and Gorski in the early 1960s.[1,2] Specific protein receptors for most of the steroid hormones have been shown to exist within uterine tissue. Initially thought to reside primarily in the cytoplasm, steroid receptors occupy a nuclear location and serve as transcription factors for their receptive ligands.[3,4] Since those early days of steroid hormone research, the complexity of the mechanism of action of steroids has continued to expand. Different isoforms of the estrogen and progesterone receptors have been identified.[5–8] Actions of steroids have been shown to involve membrane as well as nuclear receptors.[9] Modulation of steroid action by growth factors and cytokines has been identified.[10,11] Paracrine interactions between cell types suggest that steroid interactions can be direct or indirect.[12–14] More recently, accessory proteins that stabilize or destabilize the transcriptional complex involved in steroid hormone actions have been described.[15,16] These repressors and coactivators, as they are called, further extend our understanding of the role of steroid hormones in target cells. Indeed, inhibition of gene expression may be as important a phenomenon during cellular differentiation as stimulation of specific genes. All of these features come into play during the highly intricate endometrial cycle that leads to the establishment of uterine receptivity during the mid-secretory phase.

In the current issue of the *Journal*, Vienonen and colleagues investigate an inclusive list of nuclear receptors and cofactors in human endometrium and myometrium. This is an important and thorough study, providing an in-depth examination of many of the steroid receptors, including glucocorticoid receptor, androgen receptors (AR), estrogen receptors (ERα and ERβ), progesterone receptors A and B, vitamin D receptor (VDR), and retinoic acid receptors (RAR), as well as several cofactors that are important in steroid action. Using real-time polymerase chain reaction, the authors corroborate earlier studies demonstrating cyclic regulation of ERα and ERβ, AR, and progesterone receptors A and B, but little regulation of the glucocorticoid receptor. Although functionality of the receptors and accessory proteins is not addressed, the finding of both constitutive and regulated proteins, including RAR isoforms, is fascinating and potentially important, especially because secretory phase progesterone action has been tied to this other steroid receptor.[17] In line with recent reports, the expression of coactivators was not significantly regulated. This study sets the stage for further investigation of cofactor and steroid receptor expression in various gynecologic disorders and raises many important issues for consideration of those future investigations.

Altered expression of endometrial regulatory proteins has been postulated as an underlying cause of infertility and recurrent pregnancy loss and as a contributing factor leading to neoplastic growth within the reproductive tract, including uterine fibrioids, endometriosis, and uterine cancers. Recent endometrial gene profiling studies illustrate the intricate downstream effects of ovarian steroids and the exquisite complexity of gene expression profiles over the course of the menstrual cycle.[18,19] These patterns of gene expression may be significantly altered in certain disease states. Comparison of the endometrium from women with and without endometriosis suggests a wide disparity in gene expression, consistent with an overall progesterone insensitivity.[20] Suppression of endometriosis appears to correct such defects.[21] What forms the basis for this altered action of progesterone? Possibly this is a byproduct of an altered pattern of receptor or coactivator expression in response to the inflammatory milieu of the disease.

Another striking example of enhanced endometrial responsiveness to estrogen and androgens is seen in polycystic ovarian syndrome (PCOS). These patients also exhibit significant variations in gene expression compared with normal fertile controls (Groll et al, Society for Gynecologic Investigation, abstract, 2003). In this common endocrine condition, miscarriage rates are high and cycle fecundity is low.[22] Elevated AR[23] and ERα and steroid receptor coactivators[24] have been specifically demonstrated in the endometrium of women with this disorder compared with normal fertile controls. Purposeful over-expression of coactivators, such as TIF2 and AIB1 in vitro, demonstrate a marked increase in estrogen sensitivity, even in response to weak estrogens (Groll et al, ASRM abstract, 2003). Correction of such defects is the subject of ongoing investigation.

The identification of all the receptors and cofactors in the endometrium alone will not be sufficient to elucidate their function. Collectively, we will have our hands full as we try to tease out the details of regulation and interaction between multiple receptors, coactivators, and repressors within complex tissues. Applying this information to the clinical arena will require further investigation. Cancer risk and prevention are clearly at the top of the list as we consider where to take the next generation of studies of steroid receptor coactivators and repressors. Women with PCOS who exhibit elevated ERα and steroid receptor coactivators may be at heightened risk of endometrial hyperplasia or cancer. The rapidly growing

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1071-5576/04/$30.00
doi:10.1016/j.jsgi.2003.11.001

leiomyomata might exhibit increased sensitivity to steroid hormones. Response of cancers to chemotherapy and selective estrogen modulators may depend on the complement of receptor isoforms and coactivators that are expressed within that cell. Heterogeneity of cofactors might allow selection for aberrant growth or resistance to hormonal therapy. Other gynecologic disorders will undoubtedly be found that are ultimately dependent on derangements in steroid receptors and cofactor expression.

To investigate the interactions of coactivators and receptors in the reproductive tract, directed transfection of nuclear cofactors and gene knockout studies will be a valuable approach coming from the laboratory, whereas inspection and comparisons of defined subsets of infertile or abnormal endometrium will provide a valuable clinical approach. Medical management with pharmaceuticals that alter the estrogen, progesterone, or androgen milieu will also share the stage to address new therapeutic approaches that restore normal physiology to women with infertility or recurrent pregnancy loss. Development and applications of new selective estrogen, progesterone, and androgen modulators will also evolve faster with our growing understanding of how receptors and nuclear cofactors interact. Discovery of the molecular biology of this interaction will likely lead to new drugs and a new generation of hormonal antagonists. The impact of new powerful drugs will likely provide a way to selectively modulate the activity of steroid receptors within selected target tissues, such as breast, bone, and uterus. Combinations of hormones and selective estrogen modulators are already showing utility.

The study of steroid action in human target tissues is a moving target. The tale of how steroids work at the cellular level is a story that keeps getting better. Paraphrasing Kreb, the only thing keeping us from understanding nature is its sheer complexity. The study by Vienonen moves us closer to that goal.

REFERENCES

1. Jensen EV, Jacobson HI. Basic guides to the mechanism of estrogen action. Recent Prog Horm Res 1962;18:387–409.
2. Gorski J, Toft D, Shyamala G, Smith D, Notides A. Hormone receptors: Studies on the interaction of estrogen with the uterus. Recent Prog Horm Res 1968;29:45–73.
3. King WJ, Greene GL. Monoclonal antibodies localize oestrogen receptor in the nuclei of target cells. Nature 1984;307:725–??.
4. Welson WV, Liberman ME, Gorski J. Nuclear localization of unoccupied oestrogen receptors. Nature 1984;307:747–??.
5. Nilsson S, Kuiper G, Gustafsson JA. ERβ: A novel estrogen receptor offers the potential for new drug development. Trends Endocrinol Metab 1998;9:387–95.
6. Katzenellenbogen BS, Montano MM, Ediger TR, et al. Estrogen receptors: Selective ligands, partners and distinctive pharmacology. Recent Prog Horm Res 2000;163–93.
7. Lessey BA, Alexander S, Horwitz KB. The subunit structure of human breast cancer progesterone receptor: Characterization by chromatography and photoaffinity labeling. Endocrinology 1982; 112:1267–73.
8. Wei LL, Gonzalez-Aller C, Wood WM, Miller LA, Horwitz KB. 5′-Heterogeneity in human progesterone receptor transcripts predicts a new amino-terminal truncated "C"-receptor and unique A-receptor messages. Mol Endocrinol 1990;4:1833–40.
9. Welter BH, Hanson EL, Saner KJ, Wei J, Price TM. Membrane-bound progesterone receptor expression in human aortic endothelial cells. J Histochem Cytochem 2003;51:1049–55.
10. Nelson KG, Takahashi T, Bossert NL, Walmer DK, McLachlan JA. Epidermal growth factor replaces estrogen in the stimulation of female genital-tract growth and differentiation. Proc Natl Acad Sci U S A 1991;88:21–5.
11. Somkuti SG, Yuan LW, Fritz MA, Lessey BA. Epidermal growth factor and sex steroids dynamically regulate a marker of endometrial receptivity in Ishikawa cells. J Clin Endocrinol Metab 1997;82:2192–7.
12. Brisken C, Park S, Vass T, Lydon JP, O'Malley BW, Weinberg RA. A paracrine role for the epithelial progesterone receptor in mammary gland development. Proc Natl Acad Sci U S A 1998; 95:5076–81.
13. Lessey BA. Two pathways of progesterone action in the human endometrium: Implications for implantation and contraception. Steroids 2003;In press.
14. Cooke PS, Buchanan DL, Young P, et al. Stromal estrogen receptors mediate mitogenic effects of estradiol on uterine epithelium. Proc Natl Acad Sci U S A 1997;94:6535–40.
15. Shibata H, Spencer TE, Onate SA, et al. Role of co-activators and co-repressors in the mechanism of steroid/thyroid receptor action. Recent Prog Horm Res 1997;141–64.
16. Molenda HA, Kilts CP, Allen RL, Tetel MJ. Nuclear receptor coactivator function in reproductive physiology and behavior. Biol Reprod 2003;69:1449–57.
17. Curry TE, Osteen KG. The matrix metalloproteinase system: Changes, regulation, and impact throughout the ovarian and uterine reproductive cycle. Endocr Rev 2003;24:428–65.
18. Carson DD, Lagow E, Thathiah A, et al. Changes in gene expression during the early to mid-luteal (receptive phase) transition in human endometrium detected by high-density microarray screening. Molec Hum Reprod 2002; In press.
19. Kao LC, Tulac S, Lobo S, et al. Global gene profiling in human endometrium during the window of implantation. Endocrinology 2002;143:2119–38.
20. Kao LC, Germeyer A, Tulac S, et al. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. Endocrinology 2003;144:2870–81.
21. Surrey ES, Silverberg KM, Surrey MW, Schoolcraft WB. Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients with endometriosis. Fertil Steril 2002;78:699–704.
22. Homburg R. Polycystic ovary syndrome—From gynaecological curiosity to multisystem endocrinopathy. Hum Reprod 1996;11: 29–39.
23. Apparao KBC, Lovely LP, Gui YT, Lining RA, Lessey BA. Elevated endometrial androgen receptor expression in women with polycystic ovarian syndrome. Biol Reprod 2002;66:297–304.
24. Gregory CW, Wilson EM, Apparao KBC, et al. Steroid receptor coactivator expression throughout the menstrual cylcle in normal and abnormal endometrium. J Clin Endocrinol Metab 2002;87: 2960–6.