Viewpoint

Estrogen-*repressed* genes – key mediators of estrogen action?

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Introduction

Estrogen receptor (ER)-α is a member of the nuclear receptor family of transcription factors. It is regulated not only by binding to its ligand but also through interaction with co-regulators that can either enhance (coactivators) or repress (corepressors) its transcriptional activity. ER-α regulates the expression of a large number of genes, including components of the signaling, cell cycle, and anti-apoptosis pathways. A great deal of work in this area has increased our understanding of the role of ER-α in activation of genes; we now know that binding of estrogen to ER-α results in repositioning of helix 12 that allows recruitment of coactivators and thus activation of transcription. However, recent gene expression profiling by a number of groups using different model systems has revealed that the majority of estrogen-regulated genes are repressed rather than activated. This has been shown in cells cultured *in vitro* but also *in vivo*, where estrogen treatment resulted in down-regulation of a significant number of target genes. This repression was lost in ER-α-knockout mice [1], confirming that repression requires ER-α. Although estrogen-mediated repression of genes has received little attention in the past, it is likely to be critical for the role of ER-α in both normal and disease processes. Herein we discuss some important studies on repression by ER-α and try to highlight the most burning (and partially controversial) questions.

Evidence for estrogen-mediated repression of genes

There are a handful of studies that report estrogen-mediated repression of genes, with some of them also addressing potential mechanisms. For example, the ErbB2 proto-oncogene is repressed by estrogen [2]. This repression seems to result from competition between estrogen-bound ER-α and another transcription factor (most likely activator protein [AP]-2) for the coactivator steroid receptor coactivator (SRC)-1, because overexpression of SRC-1, but not SRC-2 or SRC-3, relieves repression of ErbB2. This gives rise to the question of whether estrogen-mediated repression really involves 'classical' repression, or merely represents a loss of basal transcription caused by squelching (i.e. competition for a limited pool of coactivators) or simple displacement of coactivators.

There is some evidence that corepressors can play a role in estrogen-mediated repression of genes. Overexpression of the corepressors SMRT (silencing mediator for retinoid and thyroid hormone receptors) and SAFB1 (scaffold attachment factor B1) enhanced repression of folate receptor-α [3] and E-cadherin [4], respectively. In contrast, none of the ER-α coactivators tested (including SRC family members) affected the repression of folate receptor-α by estrogen [3]. Interestingly, depletion of the corepressor DP97 attenuated the repression of ErbB2 [5]. These data suggest that corepressors are involved in repression, but is this really an active recruitment of corepressors to the promoters of target genes? Clearly, interaction of corepressors with ER-α in the presence of estrogen does not fit the classical model in which estrogen-bound ER-α interacts with coactivators, whereas antiestrogen-bound ER-α preferentially interacts with corepressors. However, based on a few studies showing that some corepressors can bind ER-α in the presence of estrogen and that coactivators and corepressors coexist in complexes, it might be timely to revisit this model.

Another open question is whether nonclassical ER-α pathways are involved in repression, just as described for estrogen-mediated induction of genes. Does ER-α have to be bound to estrogen response elements, or can it bind indirectly via interaction with other transcription factors such as Sp1, AP1, nuclear factor-κB, or CAAT-enhancer-binding protein-β? Some studies have shown that the ER-α DNA-binding domain (DBD) is necessary for the repression of certain genes whereas for others it is not required. For example, mutation of the ER-α DBD did not affect the repression of ErbB2, whereas repression of the interleukin-6 promoter was abolished [6]. Thus, repression of at least some genes seems not to require direct binding of ER-α to promoter DNA.

AP = activator protein; DBD = DNA-binding domain; ER = estrogen receptor; SRC = steroid receptor coativator.

Finally, it may be that the homolog ER-β also plays a role in estrogen-mediated repression of genes. This question has not been addressed; however, some findings, such as the interaction between estrogen-bound ER-β and corepressors, favor such an involvement [7].

Conclusion

There is little doubt that estrogen treatment can result not only in activation but also in repression of genes. Although the mechanism of estrogen-mediated repression is largely unknown, it is unlikely to be the same for all genes and may depend on many factors such as the gene promoter and cell context.

One of the critical questions is whether estrogen-bound ER-α can, directly or indirectly, actively recruit corepressors to the promoters of certain target genes to repress transcription. Ultimately, however, the most important question pertains to the biological relevance of estrogen-mediated repression; are repressed genes critical targets of ER-α that need to be turned off (or downregulated) for efficient ER-α activity? For example, is estrogen-mediated repression of tumor suppressor or apoptosis genes critical for breast cancer development and progression? Ongoing studies in a number of laboratories are expected to shed some light on this exciting area in the near future.

Competing interests

The author(s) declare that they have no competing interests.

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References

1. Hewitt SC, Deroo BJ, Hansen K, Collins J, Grissom S, Afshari CA, Korach KS: **Estrogen receptor-dependent genomic responses in the uterus mirror the biphasic physiological response to estrogen.** *Mol Endocrinol* 2003, **17:**2070-2083.
2. Newman SP, Bates NP, Vernimmen D, Parker MG, Hurst HC: **Cofactor competition between the ligand-bound oestrogen receptor and an intron 1 enhancer leads to oestrogen repression of ERBB2 expression in breast cancer.** *Oncogene* 2000, **19:**490-497.
3. Kelley KM, Rowan BG, Ratnam M: **Modulation of the folate receptor alpha gene by the estrogen receptor: mechanism and implications in tumor targeting.** *Cancer Res* 2003, **63:** 2820-2828.
4. Oesterreich S, Deng W, Jiang S, Cui X, Ivanova M, Schiff R, Kang K, Hadsell DL, Behrens J, Lee AV: **Estrogen-mediated downregulation of E-cadherin in breast cancer cells.** *Cancer Res* 2003, **63:**5203-5208.
5. Rajendran RR, Nye AC, Frasor J, Balsara RD, Martini PG, Katzenellenbogen BS: **Regulation of nuclear receptor transcriptional activity by a novel DEAD box RNA helicase (DP97).** *J Biol Chem* 2003, **278:**4628-4638.
6. Stein B, Yang MX: **Repression of the interleukin-6 promoter by estrogen receptor is mediated by NF-kappa B and C/EBP beta.** *Mol Cell Biol* 1995, **15:**4971-4979.
7. Webb P, Valentine C, Nguyen P, Price RH Jr, Marimuthu A, West BL, Baxter JD, Kushner PJ: **ERbeta binds N-CoR in the presence of estrogens via an LXXLL-like motif in the N-CoR C-terminus.** *Nucl Recept* 2003, **1:**4.