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Thoughts on tamoxifen resistant breast cancer. Are coregulators the answer or just a red herring?

J. Dinny Graham, David L. Bain, Jennifer K. Richer, Twila A. Jackson, Lin Tung, Kathryn B. Horwitz *

Department of Medicine, University of Colorado, School of Medicine, Denver, CO 80262, USA

Abstract

The antiestrogen tamoxifen is an effective treatment for estrogen receptor positive breast cancers, slowing tumor growth and preventing disease recurrence, with relatively few side effects. However, many patients who initially respond to treatment, later become resistant to treatment. Tamoxifen has both agonist and antagonist activities, which are manifested in a tissue-specific pattern. Development of tamoxifen resistance can be characterized by an increase in the partial agonist properties of the antiestrogen in the breast, resulting in loss of growth inhibition and even inappropriate tumor stimulation. Nuclear receptor function is modulated by transcriptional coregulators, which either enhance or repress receptor activity. Using a mixed antagonist-biased two-hybrid screening strategy, we identified two such proteins: the human homolog of the nuclear receptor corepressor, N-CoR, and a novel coactivator, L7/SPA (Switch Protein for Antagonists). In transcriptional studies N-CoR suppressed the agonist properties of tamoxifen and RU486, while L7/SPA increased agonist effects. We speculated that the relative level of these coactivators and corepressors might determine the balance of agonist and antagonist properties of mixed antagonists such as tamoxifen. Using quantitative RT-PCR we therefore measured the levels of transcripts encoding these coregulators, as well as the corepressor SMRT, and the coactivator SRC-1, in a small cohort of tamoxifen resistant and sensitive breast tumors. The results suggest that tumor sensitivity to mixed antagonists may be governed by a complex set of transcription factors, which we are only now beginning to understand.

Keywords: Steroid receptors; Estrogen receptors; Progesterone; Breast neoplasms; Transcriptional coregualtors; Tamoxifen

The antiestrogen tamoxifen is the most commonly used and effective treatment for patients with estrogen receptor (ER)-positive breast cancers. As an adjuvant for primary breast cancer, treatment with tamoxifen improves disease-free and overall survival rates [1] and in metastatic disease tamoxifen induces remission of ER-positive tumors [2,3]. Most recently, tamoxifen has been shown to prevent breast cancers in women at high risk of developing this disease [4]. Thus in various settings, tamoxifen is an inhibitory ER ligand in the breast, and this property explains both its efficacy and its widespread use.

However, almost without exception, breast cancers that initially respond well to tamoxifen by growth cessation or regression, eventually resume growing despite continued presence of the antagonist. How can this 'acquired resistance' be explained? It is likely, that in some cases, loss of ER expression or increased metabolism of the drug [5–7] accounts for loss of tumor responsiveness to tamoxifen. However, in more than half of acquired resistance cases, tumor ER are retained [8] — a statistic analogous to that seen with sequential ER measurements in relapsing patients who did not receive endocrine therapy [9]. Thus, tamoxifen treatment itself, does not significantly alter ER levels [9–11]. Indeed, tamoxifen-resistant tumors remain responsive to growth inhibition by pure antiestrogens (but clinical data are sparse) and other hormonal therapies [12]. Paradoxic reports of tumor stasis and even regression after tamoxifen withdrawal in resistant patients suggest that in at least some resistant tumors, the antagonist has switched to an agonist [13–15]. This is not entirely surprising, since tamoxifen is a 'mixed' antiestrogen, having primarily antagonist effects in the

* Corresponding author. Tel.: +1-303-3158443; fax: +1-303-3154525.

E-mail address: kate.horwitz@uchsc.edu (K.B. Horwitz).

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normal breast, but acting as an agonist in normal uterus and bone. These tissue-specific properties also classify tamoxifen as a 'selective estrogen receptor modulator' or SERM. We and others have suggested that the intrinsic estrogenic activity of tamoxifen observed in some normal tissues, may also account for acquired resistance in some breast cancers, resulting in inappropriate stimulation of tumors (reviewed in [16–19]). New molecular studies of steroid receptors provide insights into mechanisms by which this may occur. However, they raise other questions to which we do not yet have answers.

ER, the direct targets of tamoxifen, are members of the nuclear receptor family of ligand activated transcription factors. In response to ligand, ER dimerize and bind to DNA response elements on the promoters of target genes to regulate transcription [20]. The extent and direction of gene regulation by ER is influenced not only by the types of ligands bound, but also by specific coregulatory proteins, present at rate-limiting levels in the nucleus, that are recruited to, and interact with promoter-bound receptor-ligand complexes [21–23]. These coregulatory proteins can be either coactivators, which enhance transcription, or corepressors which suppress it.

A number of coactivators are known to interact with agonist-occupied ER to enhance transcription. These include the p160 family of related coactivators (SRC-1, GRIP1/TIF2 and AIB1/RAC3/ACTR/p/CIP, refs [24–27]), CREB-binding protein CBP/p300 [28], and p/CAF, the CBP/p300-associated factor. These proteins form multiple contacts with ER and each other, to produce multi-protein cooperative coactivator complexes capable of synergistically activating estrogen-driven transcription (reviewed in [22,26,28,29]). The complex has at least dual functions; it possesses histone acetyl-transferase activity [30–32], which facilitates chromatin remodeling, and it binds proteins of the basal transcriptional machinery [33]. Like estradiol, the partial agonist transcriptional activity of tamoxifen appears also to be enhanced by coactivators. These include, in addition to p160 family members [34], a novel coactivator termed L7/Switch Protein for Anatagonists (L7/SPA; [35]). Unlike the p160 family of proteins, the action of L7/SPA is specific for mixed antagonists; it does not enhance the activity of estradiol-bound ER or progesterone-bound progesterone receptors (PR).

Two nuclear receptor corepressors have been identified to date: N-CoR (nuclear receptor corepressor) [36] and SMRT (silencing mediator for retinoid and thyroid receptors)/TRAC-2 [37,38]. Both were initially characterized on the basis of their ability to bind members of the thyroid and retinoid receptor family of nuclear receptors in the absence of ligand, and repress transcription. In addition to associating with these nuclear receptors on DNA, N-CoR and SMRT form complexes with the mammalian repressor mSin3 and with histone deacetylases ([39–41], and reviewed in [42]), which together repress chromatin structure and block transcription. Unlike the unliganded thyroid/retinoic acid family of nuclear receptors, neither unliganded steroid receptors, nor agonist-bound ER and PR bind N-CoR or SMRT. Thus, under physiological circumstances, there are no known associations between steroid receptors and transcriptional corepressors.

To test the hypothesis that mixed antagonists, like tamoxifen or the antiprogestin RU486, have inappropriate agonist-like effects in certain tissues or tumors, we postulated that transcriptional coregulators are inadvertently brought to the promoters of DNA-bound, antagonist-occupied receptors, and set out to isolate such factors. Initially, the PR C-terminus, consisting of the hinge and hormone binding domain of the receptors was used as bait in a two-hybrid screen of a HeLa cDNA library, in which the yeast cells were treated with saturating concentrations of RU486 [35]. Thus we biased the system in an attempt to isolate factors that preferentially interact with antagonist-occupied receptors. We isolated several interesting proteins that regulate transcription by antagonist-occupied receptors in opposite directions. One was L7/SPA, a previously described 27 kD protein containing a basic region leucine zipper domain at its N-terminus, through which it forms stable homodimers that bind to RNA and double-stranded DNA (reviewed in [35]). A Green-Fluorescent-Protein-L7/SPA chimera localizes to the nucleus. When coexpressed with tamoxifen-occupied ER, or RU486-occupied PR or glucocorticoid receptors (GR), L7/SPA increases the partial agonist activity of the antagonists by 3 to 10-fold. Importantly, it has no effect on agonist-mediated transcription involving estradiol, progesterone or dexamethasone. The interaction of L7/SPA with PR maps to the hinge region of the receptors, and indeed, the isolated PR hinge region squelches, or inhibits, L7/SPA-dependent increases in transcription by tamoxifen [35]. This protein does not bind to the hinge region via the LXXLL motifs characteristic of coactivators that bind at activation function 2 of the hormone binding domain. Interestingly, transcription by pure antagonists which lack partial agonist actions, such as the pure antiestrogen ICI164,384 or the pure antiprogestin ZK98299, can not be upregulated by L7/SPA. Therefore, this coactivator appears to up-regulate specifically, that component of transcription activatable by mixed antagonists [35].

In the same protein–protein interaction screen in which L7/SPA was isolated, we also isolated a C-terminal human (h) cDNA fragment that turned out to be homologous to the mouse (m) N-CoR whose sequence had been published several weeks earlier [37]. We cloned and sequenced the entire human N-CoR coding sequence, and compared it with the murine coding

sequence. In addition to a 7359 nucleotide open reading frame that predicts a 2453 amino acid protein, two apparent N-terminal splice variants that result in loss of amino acids 83-206 and amino acids 83-147 in the N-terminal repressor domain, were detected in the human transcripts. The amino acid identity between mN-CoR and hN-CoR is high (98.9%), with the greatest divergence observed in the second repressor domain, in which the identity falls to 80.4%. Binding of hN-CoR maps to the PR hormone binding domain. We found that mN-CoR, and the related human corepressor, SMRT suppress the partial agonist activity of RU486 or tamoxifen by more than 90%. This suppression is completely squelched by overexpression of the transcriptionally silent PR C-terminus. These studies represented the first demonstration that antagonist-occupied steroid receptors can recruit corepressors to the transcription complex [35]. They suggest that the effects of antagonist ligands are not passive — i.e. that they do not simply prevent transcription by blocking binding and activation of receptors by agonists. Instead, these studies suggest that repression by antagonists can be an active process, generated via recruitment of corepressor molecules to the transcriptional machinery, by antagonist-receptor complexes. In this scenario, steroid antagonists can theoretically suppress transcription even in the absence of the cognate agonists. For example, antagonists may suppress transcription of a gene whose promoter contains a steroid response element, but which is activated by growth factor signaling pathways that regulate the same promoter. This would explain observations of breast tumor growth suppression by antagonists, which occur even in the absence of the agonist.

Additional studies demonstrated that corepressors can reverse the transcriptional activation produced by antagonist ligands in the presence of the coactivator, L7/SPA [35]. This suggested to us, that the relative levels of coactivators vs corepressors may determine whether the agonist or antagonist effects of these mixed antagonists predominate in a tissue or tumor. Although there is clearly functional redundancy among coregulatory proteins, there is evidence to suggest that their expression levels are rate-limiting, and therefore, that their relative levels may determine the outcome of ligand signaling in a cell. Specifically, with respect to tamoxifen resistant breast cancers, we hypothesized that the levels of expression of coactivators versus corepressors in a tumor would dictate whether tamoxifen exerts agonist- or antagonist-like activity. For example, under conditions of coactivator excess, in which the agonist-like activity predominates, the tumor would respond inappropriately to tamoxifen. Such a tumor would present with a 'resistant' phenotype, yet would actually be responding to tamoxifen, albeit as an agonist. To test this idea we have begun measuring transcript expression levels of several coregulators in breast tumors known to be tamoxifen sensitive or resistant. We have developed a sensitive, quantitative reverse transcription–polymerase chain reaction (RT-PCR) protocol to measure mRNA levels encoding the corepressors N-CoR and SMRT and the coactivators L7/SPA and SRC-1. This assay accurately measures the extremely low levels of these factors present in small amounts of tumor material in a set of tumors in which the tamoxifen-response status has been defined. The studies are ongoing, but our preliminary data indicate that corepressor levels may be more important than coactivator levels. Additionally, the studies indicate that mechanisms of corepressor binding to steroid receptors may differ from their binding to thyroid/retinoic acid receptors. This could have been predicted, given the fact that steroid receptors are not natural targets of corepressor activity. Rather, their recruitment to antagonist-occupied steroid receptors may represent a pharmacologic anomaly [43].

It is our opinion, that the full complement of coregulatory proteins that could influence the direction of transcription by antagonist-occupied steroid receptors has yet to be completely identified. L7/SPA is the only antagonist-specific coactivator defined to date. We doubt that it is the only, or even the most important, protein to have this property. Similarly, it is unlikely that SMRT and N-CoR are the only corepressors that interact with antagonist-occupied steroid receptors. We believe that these three coregulators represent a minor subset of the whole, for several reasons. First, screening for coregulators has, for the most part, been limited to proteins that interact with the C-terminal ligand binding domain of the receptors at activation function 2. However, activation function 1, located in the N-terminus of the receptors, may be as important, if not more important for the agonist properties of steroid antagonists, but this region has received little attention as a target for coregulatory protein binding. Newer experimental strategies may correct this deficiency [44,45]. Second, recent crystallographic analyses of steroid receptor ligand binding domains show that there are subtle structural variations in the conformation of receptors resulting from the binding of different ligands [46,47]. This would yield multiple, subtly different targets on the C-terminal surface of the receptors, for the binding of a variety of coregulators, dictated specifically by the identity of the ligand. As discussed above, few, if any, ligand-specific coregulators have yet been identified, perhaps because multiple ligands have not been compared in screening assays. Third, while C-terminal receptor structure has been analyzed in detail, little is known about the structure of steroid receptor N-termini. Yet, to judge from PR [48], this region has an ordered but asymmetric structure, that would offer multiple potential target sites for protein–protein inter-

actions. The structure of steroid receptor N-termini appears to be influenced by the DNA binding domain, and possibly, also by DNA binding-induced allostery. Putative recruitment of coregulatory proteins could therefore occur either through induced fold mechanisms generated by direct contact between the coregulators and the receptors at various sites along the N-terminus, or through structural alterations in the N-terminus (followed by binding of different coregulators) induced by DNA binding. The latter in particular, suggests a scenario in which different coregulators interact with receptors, depending on the gene to which the receptors are bound. Existence of such heterogeneity is suggested by the known tissue specificity of antagonists. For example, the usefulness of tamoxifen in breast cancer is due to its predominantly antagonist nature in the breast. However, in the uterus it is a potent estrogen, where, like estradiol (when unopposed by progesterone) it can induce epithelial hyperplasia and endometrial cancers. Are tamoxifen's mixed agonist/antagonist properties due to (i) activation of different sets of genes in the breast vs uterus; (ii) the presence of different sets of coregulators in each tissue; (iii) varying and limiting levels of coregulator subsets in each tissue; or (iv) differential utilization of a common set of coregulators whose recruitment to the receptors is controlled by the identity of the ligand and by variable DNA structure at different gene loci?

The answers to these questions have important implications for our understanding of acquired tamoxifen resistance in breast cancer. Mechanism (i) above is likely to be the case, as gene array technology is beginning to show. On the other hand, to date, no tissue-specific coregulators have been described. Quite the contrary, all known coregulators are 'ubiquitous'. This suggests that mechanism (ii) may not be critically important, and if anything, that number (iii), which addresses the relative levels of coregulators, is more important. However, this scenario does not address the redundancy issue. Namely, the possibility that one coregulator can functionally replace another. Coregulator redundancy is suggested by SRC-1 knockout studies, which generated only subtle phenotypes in the SRC-1 deficient mice [49]. If the same coregulator complement and redundancy exists in breast cancers, it will, we believe, make it very difficult to correlate tamoxifen resistance with coregulator levels. That leaves scenario number (iv) above as a likely player in tamoxifen resistance — an extraordinarily complex one.

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