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Progesterone Receptors, their Isoforms and Progesterone Regulated Transcription

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Abstract

This review discusses mechanisms by which progesterone receptors (PR) regulate transcription. We examine available data in different species and tissues regarding: 1) regulation of PR levels; and 2) expression profiling of progestin-regulated genes by total PRs, or their PRA and PRB isoforms. 3) We address current views about the composition of progesterone response elements, and postulate that PR monomers acting through "half-site" elements are common, entailing cooperativity with neighboring DNA-bound transcription factors. 4) We summarize transcription data for multiple progestin-regulated promoters as directed by total PR, or PRA *vs.* PRB. We conclude that current models and methods used to study PR function are problematical, and recommend that future work employ cells and receptors appropriate to the species, focusing on analyses of the effects of endogenous receptors targeting endogenous genes in native chromatin.

I. INTRODUCTION

Like all nuclear receptors, progesterone receptors (PR) are transcription factors that consist of a DNA binding domain (DBD), sandwiched between an upstream N-terminal region that contains activation (AF) and inhibitory (IF) functions, and a downstream hinge region and C-terminal ligand binding domain (LBD) (Hovland *et al*, 1998). There are two PR isoforms, PRA and PRB, which differ only in that human PRB contain an additional 164 amino acid far N-terminal region called the "B-upstream segment" (BUS) that confers AF3 activity. BUS is missing in PRA (Sartorius *et al*, 1994b). Site-specific mutations of amino acids in BUS that are responsible for its AF3 activity destroy PRB-specific gene regulation without however, switching PRB to PRA (Tung *et al*, 2006). This suggests that global structural differences between PRB and PRA apart from BUS control their unique properties. We review below the distinctive transcriptional activities of the two PR isoforms.

In normal human tissues including the breast, PRA and PRB are generally expressed at similar levels but at least in some breast cancers, their ratio is dysregulated (Graham *et al*, 1995b; Hopp *et al*, 2004). Classically, transcription mediated by PR is viewed as follows: 1) The unliganded receptors are cytoplasmic and bound to heat shock proteins in the absence of progestins (P). 2) Liganded receptors are released from heat shock proteins, dimerize and translocate to the nucleus. 3) There they locate specific palindromic DNA binding sites called progesterone response elements (PREs) in promoters of PR regulated genes, after which, 4) transcription is initiated through recruitment of a transcription complex. While this may be the case for some tissues, in some contexts, on some promoters, this simple model cannot explain data showing that: 1) PR are largely localized to the nucleus even in the

absence of P; 2) dimerization may not be required for PR mediated transcription; 3) the endogenous structures of PREs have not been defined by unbiased *in vivo* analyses but are unlikely to be "classical"; and 4) PR also signal through cell membrane and cytoplasmic pathways.

The functions of steroid receptors generally, and of PR specifically, have been studied in a variety of systems. For PR, the most widely used are artificial reporters consisting of tandem palindromic PREs separated by random intervening sequences, linked to luciferase. These double PRE (PRE2) reporters are then transiently or stably transfected into cells that may or may not be relevant to the question under study; conditions and cells are optimized to yield maximum luciferase activity; and conclusions are drawn regarding PR structure, PR function, PR isoform specificity, and coregulators of PR-dependent transcription. In an attempt to address more physiologically relevant conditions, other studies choose *bona fide* genes regulated by PR, map their proximal promoters (usually less than 5 Kb) by deletion analysis, and search for classical PREs within regions considered to be functionally important. To confirm the validity of any conclusions, candidate sequence(s) are subjected to protein:DNA interaction studies by electrophoretic mobility shift assays, DNA footprinting, or methylation interference; all of which use "naked" DNA. More recently, nuclear receptor binding sites and kinetics of protein:DNA interactions have been analyzed by chromatin immunoprecipitation (ChIP), which has the advantage of searching for PR binding sites in the context of chromatin. However, even ChIP assays are biased by being limited to a search of specified DNA regions or sequences. The least biased methods are ChIP-on-chip, which combines ChIP with microarray technology (chip) and identifies DNA-binding sites on a genome-wide basis; or ChIP-*seq*, which combines ChIP with massively parallel DNA sequencing. Studies examining PR-regulated promoters have, as of this writing, been limited to proximal promoter regions using ChIP assays. Neither ChIP-on-chip nor ChIP-*seq* has been reported. Thus many important PR regulatory regions including ones in introns, 3′ untranslated regions (UTR), or tens of thousands of Kb removed from transcriptional start sites remain unexamined, and true endogenous DNA sequences to which PR bind either directly or indirectly remain largely unknown.

In this review we examine available data in a variety of tissues and species addressing: 1) regulation of PR levels by estrogenic and non-estrogenic signaling; 2) analysis of genes regulated by total PR, or by PRA *vs.* PRB using expression profiling; 3) our current understanding about the composition of PREs, and transcriptional regulation *via* PR monomers, PRE half-sites and cooperativity with other transcription factors. 4) We review in detail transcriptional regulation of multiple P-regulated promoters by total PR and the two PR isoforms. Although many signaling pathways converge on PR and influence their transcriptional activity (reviewed in (Daniel *et al*, 2009)), even in the absence of ligands (Jacobsen *et al*, 2005), and non-genomic effects of PR have also been described (Boonyaratanakornkit *et al*, 2001), this review is limited to the genomic transcriptional effects of liganded PR.

II. REGULATION OF PR EXPRESSION

To understand PR function, it is important to review factors that regulate PR levels. In T47D human breast cancer cells, which are the major models for human PR, synthesis of the PRA and PRB isoforms is driven by transcription from two promoters (Kastner *et al*, 1990) located at −711 to +31 and +464 to +1105 of the transcription start-site, respectively. At least 6 transcripts encode PR (Kastner *et al*, 1990; Wei *et al*, 1988) containing translational start sites not only for PRA and PRB, but also for at least one N-terminally truncated protein called PRC (Condon *et al*, 2006; Wei *et al*, 1990). The majority of normal human P target tissues that have been studied express PRA and PRB in equimolar amounts (Graham &

Clarke, 1997) generating 3 theoretical receptor populations consisting of 25% PRA homodimers, 25% PRB homodimers and 50% PRA/PRB heterodimers. Fluorescence resonance energy transfer microscopy, which quantifies the separation distance between two molecules within nanometers, shows the presence of two closely neighboring PR molecules, which could be monomers or dimers, in transcriptionally active foci of P-treated living cells (Arnett-Mansfield *et al*, 2007; Mote *et al*, 2007).

Unlike normal human tissues, human malignancies frequently display aberrant PRA:PRB ratios (reviewed in (Mote *et al*, 2007)). Additionally, non-human but nevertheless important mammalian models used for cancer studies often have isoform ratios that differ from those in human tissues. Typically the ratio of PRA:PRB in normal mature tissues of mice and rats is 3:1 (Ilenchuk & Walters, 1987; Schneider *et al*, 1991), suggesting that the unknown factors regulating equimolarity in humans differ substantially in rodents. Additionally, this raises questions about the importance or lack thereof of equimolarity, and, if equimolarity is important, about the use of rodent models to study human progesterone physiology and disease processes.

a. E-dependent regulation of PR

The major factors that regulate PR levels in a variety of cells and tissues are 17β-estradiol or related estrogens (E) bound to estrogen receptors (ER). PR are E regulated in the uterus including the endometrium, in the pituitary and brain, and in the mammary gland/breast and other tissues (reviewed in (Graham & Clarke, 1997)). Thus it is rare that normal PR-positive cells do not also express ER. Indeed to our knowledge, discordance between PR and ER expression has only been reported in cancers.

In human breast cancer cells, the proximal promoters controlling PRA and PRB transcription contain estrogen response elements (EREs) recognized by ER, plus binding sites for other transcription factors with which ER interact (Horwitz *et al*, 1978; Kastner *et al*, 1990). For example, in MCF7 cells, liganded ER interact with an ERE ½ site within the l Kb PR promoter region (Petz *et al*, 2004a) that also contains SP1 sites (Schultz *et al*, 2003), and two different Fos/Jun AP1 binding sites, one of which functions as an activator, one as a repressor of ER regulated transcription (Petz *et al*, 2002; Petz *et al*, 2004b). ER-dependent upregulation of PR also likely involves long range transcriptional mechanisms as the region 311 Kb upstream and 4 Kb downstream of the PRB transcription start site contains 8 EREs that bind ERα (Boney-Montoya *et al*, 2010). These variable regulatory elements suggest possibilities for tissue and PR isoform-specificity. While the PR isoform-specificity controlled by ER *via* these sites has not been examined, E more strongly induces PRB than PRA in T47D (Graham *et al*, 1995a; Vienonen *et al*, 2002) and ZR-75-1 human breast cancer cells (Vienonen *et al*, 2002), but more strongly induces PRA in MCF7 breast cancer cells (Vienonen *et al*, 2002). GATA3, often expressed in association with ER, also plays a role in E mediated induction of PR transcripts (Eeckhoute *et al*, 2007). However, questions have been raised about E regulation of PR in normal breast epithelium, since total PR levels do not vary during the hormone fluctuations associated with the menstrual cycle (Mote *et al*, 2002). Other signaling pathways regulating PR include retinoic acid receptors (Clarke *et al*, 1991; Clarke *et al*, 1990) and P themselves, which promote PR downregulation (Alexander *et al*, 1989; Ghatge *et al*, 2005) and block E-dependent PR upregulation (Graham *et al*, 1995a). Methylation of the PR promoter correlates with silencing of PR expression in MCF7 cells (Xu *et al*, 2004).

As with human PR, rat PR expression is driven by two functionally distinct promoters, one proximal (+461/+675) controlling PRA, and one distal (−131/+65) controlling PRB (Kraus *et al*, 1993). Rat and human PR promoters are ~60% homologous (Kraus *et al*, 1993), and show important differences in their regulation. In contrast to the two human promoters, both

of which are E inducible in breast cancer cells (Kastner *et al*, 1990), only the proximal PRA rat promoter is E inducible in MCF7 cells. When transfected into primary rat uterine cells, the rat proximal promoter is not E regulated unless 1 additional exogenous ERE is introduced, and the distal promoter requires 2 additional exogenous EREs. In mouse pituitary 3T3 cells E induction of the rat promoters requires 2 additional EREs each. Examination of the rat promoters show the presence of 4 imperfect EREs in the 5′ flanking region and within the first exon, and ERE ½ sites are located within 150 bp of 3 of these 4 EREs, implicating ERE ½ sites in conjunction with imperfect EREs in regulating rat PR levels (Kraus *et al*, 1994).

Expression of mouse PR has been examined *in vivo* during mammary gland development using the LacZ gene encoding β-galactosidase knocked into the PR locus on one allele. While PR are highly and uniformly expressed in terminal end buds of 5 and 8 week-old intact virgin mice, in 16 week-old sexually mature cycling mice, PR expression is variegated, analogous to the effects of E + P treatment in ovariectomized mice (Ismail *et al*, 2002). Of note is that only PRB expression was monitored in this study since the LacZ knockin disrupted the translational start site for PRA. Other studies (Aupperlee & Haslam, 2007; Aupperlee *et al*, 2005; and Kariagina *et al*, 2007) raise doubt that E regulates PRB in rodents. Rabbits are seemingly even more different than the above species since they express only PRB driven by a single promoter that lacks an ERE in the 5′ flanking region, but contains an ERE that overlaps with the translational start site (Savouret *et al*, 1991). This ERE also mediates P-dependent PR downregulation (Savouret *et al*, 1991).

This brief summary highlights the species-specific effects of cell types and promoters in controlling PR expression. One can only conclude that results from most studies are not generalizable, and that at the very least, studies intended to address human biology need to employ human PR in human cells.

b. Non E-dependent regulation of PR

Estrogens do not control PR expression in all tissues. For example, E do not induce PR transcripts in primary rat granulosa cells; rather PR levels are regulated by cAMP and gonadotropins (Park-Sarge & Mayo, 1994). Similarly, PR are not directly regulated by E in rat preovulatory granulosa cells (Clemens *et al*, 1998) but are instead induced by FSH, LH and forskolin (all of which increase cAMP); an effect mediated in part by SP1/SP3 binding sites in the proximal PR promoter (Sriraman *et al*, 2003). Even in human breast cancer cells, in which E regulation of PR has been documented for at least 3 decades and forms the basis for clinical assays to predict hormone responsiveness, factors other than ER play a role. For example, in MCF7 cells, activators of protein kinase A (PKA), stimulate cAMP production, which increase PR protein levels (Cho *et al*, 1994). Interestingly PKA activators increase only PR protein not PR transcripts, while E increase both (Cho *et al*, 1994) suggesting that the cAMP targets are post-translational. The effects of cAMP are inefficient, raising PRB to 8% and PRA to 51% of the levels raised by E (Kraus *et al*, 1993). However, these results suggest possible mechanisms for differential PR isoform regulation in mice, rats and human cancer cells.

Many studies addressing regulation of human PR levels use cultured cell lines, and it is therefore of considerable importance that serum factors modify the effects observed. Sera-reduced media increase PR, suggesting that serum growth factors are inhibitory. Indeed, both IGF1 and EGF inhibit PR levels in MCF7, ZR-75-1 and T47D cells through pathways that involve PI3K/AKT/mTOR signaling (Cui *et al*, 2003b). Similarly in endometrial cancer cells, both IGF1 and IGF2 inhibit PR mRNA expression, while PR levels are increased by the anti-diabetic drug Metformin, which decreases cellular cAMP production, reduces the activities of PKA and MAPK1/3, and inhibits mTOR (Xie *et al*, 2010). Since in MCF7 cells,

liganded PRB in turn upregulate growth factors such as IRS-2, which primes cells for activation by IGF1 (Cui *et al*, 2003a), this sets up a negative feedback loop in which PRs, through varied signaling pathways, suppress their own biosynthesis.

Transcription factors besides ER also regulate PR gene expression. CEBPβ is repressive (Seagroves *et al*, 2000) while P-occupied PR increase CEBPβ in human breast cancer cells (Richer *et al*, 2002) and mouse mammary glands (Aupperlee *et al*, 2009), setting up another possible negative regulatory loop. However, P-dependent regulation of CEBPβ is mouse strain specific (Aupperlee *et al*, 2009), which makes data interpretation difficult. Another transcription factor involved in regulating the PR gene, apparently specific to the human PRB promoter, is GATA5, which binds adjacent to a polymorphism (+331G/A) in the promoter to upregulate transcript levels of this isoform only (Huggins *et al*, 2006). This clearly is another mechanism by which PR isoform levels can be dysregulated in malignant cells.

Cyclin D1 enhances PR levels *via* an enhancer that binds both ER and Cyclin D1 in the 3′-UTR of the PR gene (Yang *et al*, 2010). However, a single pulse of liganded PR suppresses cyclin levels including those of Cyclin D1 (Groshong *et al*, 1997) apparently through PR and AP1 regulatory elements in the distal Cyclin D1 promoter (Cicatiello *et al*, 2004). A second P dose exacerbates this effect; another example of a P-dependent autoinhibitory loop. The fact that multiple examples exist for negative autoregulation of PR suggest that it is physiologically important that expression levels of these receptors be tightly controlled.

Lastly, the above summary details examples of factors that regulate overall PR protein levels. However, activity of the receptor proteins is controlled not only by their levels, but by post-translational modifications including phosphorylation, sumoylation, acetylation and ubiquitination, the last of which targets PR to proteasomes for degradation (Abdel-Hafiz *et al*, 2002; Daniel *et al*, 2010; Lange *et al*, 2000). These modifications exert profound effects on the functional activity of PR. For example, desumoylation increases PR activity ~10-fold (Abdel-Hafiz *et al*, 2002). Paradoxically, ligand dependent PR downregulation following ubiquitination of the receptors is required for, and coupled to, maximal PR transcriptional activity (Lange *et al*, 2000; Shen *et al*, 2001). PR activity is also modified by growth factor signaling (Lange *et al*, 1998; Richer *et al*, 1998).

II. GENE REGULATION: EXPRESSION PROFILING

In the last few years, expression profiling studies have greatly expanded our knowledge of human P-regulated genes and the role, if any, of PR homo- and heterodimers. These studies indicate that isoform-specific gene regulation by PR is largely tissue, cell type and promoter specific. As a result, since most studies use cancer cells, conclusions may not apply to normal, physiological states. PR gene regulation has been studied mainly in ER+ T47D human breast cancer cells because, typical of luminal breast malignancies, these cells express high PR levels (Ghatge *et al*, 2005; Graham *et al*, 2005; Hopp *et al*, 2004; Jacobsen *et al*, 2005; Richer *et al*, 2002). Additionally their PR are extremely stable and not subject to fluctuation in response to transient shifts in E levels commonly seen in other cells. Therefore P-regulation can be studied without the confounding effects of having to add E in order to induce or maintain PR. Cloning of a PR-negative T47D subline called T47D-Y allowed restoration of either PRA (T47D-YA cells) or PRB (T47D-YB cells) for study of each isoform in isolation (Jacobsen *et al*, 2002; Sartorius *et al*, 1994a). These models are important because they were constructed in the background of a naturally ER+PR+ cell line and would be expected to contain appropriate ancillary coregulatory factors needed for faithful PR-dependent gene regulation. ER and PR-negative cells like MDA-MB-231 transfected with PR may lack this competence.

In the T47D models, PRA and PRB regulate some overlapping genes but most are isoform specific. An early study using incomplete gene chips described 94 P-regulated genes: 25 regulated by both PR, 64 by PRB only, 4 by PRA only (Richer *et al*, 2002), suggesting at least some differences between the two PR isoforms in sequence recognition and/or interactions with other transcription factors. A subsequent study with larger chips defined 337 P-regulated genes: 25 by both PR, 229 by PRB and 83 by PRA (Tung *et al*, 2006). Thus the trends in both studies were similar with substantially more genes uniquely regulated by liganded PRB than PRA, and relatively few by both isoforms. When both isoforms were regulatory, PRB were usually stronger transactivators than PRA (Jacobsen *et al*, 2005; Richer *et al*, 2002). This differs from the unliganded receptors where PRA are the stronger transactivators (Jacobsen *et al*, 2005). The above studies would seem to demonstrate that both heterodimers and homodimers are capable of gene regulation. A role for heterodimers has not however, been formally proven since in the T47D models homodimers are always in the mix.

Expression profiling of P-regulated genes in ER and PR-negative MDA-MB-231 cells transfected with both PR isoforms has also been reported (Leo *et al*, 2005), as have P studies in estrogenized MCF7 cells (Leo *et al*, 2005; Purmonen *et al*, 2008). Comparisons of genes among these studies are complicated by differing experimental variables, assorted time-points of P treatment, different genomic platforms, and natural *vs*. synthetic P usage. Synthetic progestins are largely similar to progesterone in terms of genes regulated in breast cancer cells (Bray *et al*, 2005; Ghatge *et al*, 2005), the exception being medroxyprogesterone acetate (MPA), which is a potent mixed progestin/androgen, and in cells that contain both PR and androgen receptors (AR), signals through both receptors (Ghatge *et al*, 2005).

Expression profiling has also been performed in T47D cells in which the PRA:PRB ratio can be altered by allowing PRA to fluctuate from 1:1 to 5:1 (Graham *et al*, 2005; McGowan & Clarke, 1999). After short P exposure (6 hrs) neither increase of the PRA:PRB ratio, nor the heightened PR levels generated by PRA overexpression, impacted the gene profiles. Interestingly, many of the early genes were transcription factors. At 48 hrs, 6-fold more genes and different functional pathways were regulated. The authors postulate that these late genes are indirect targets. However, the major lesson of this study was that the isoform ratio did not appear to be important at either timepoint. This and other studies also failed to demonstrate the dominant negative effects of PRA on PRB-dependent transcription (a phenomenon previously reported using exogenous reporters) unless PRA exceeded PRB by >15-fold (Graham *et al*, 2005; McGowan & Clarke, 1999). Such discordant ratios are rarely, if ever, observed in natural cells.

There is little overlap among P-regulated genes in normal human breast explants *vs.* T47D breast cancer cells grown as organoids (Graham *et al*, 2009), or in PRA+ mouse mammary organoids *vs*. PRA+ breast cancer cells (Santos *et al*, 2009). This emphasizes again how difficult it is to generalize among different models. Other cell types in which P-regulated genes have been analyzed include normal human breast epithelium (Graham *et al*, 2009) and the normal mouse mammary gland (Fernandez-Valdivia *et al*, 2008). These genesets have not been compared to each other or to other published datasets. Recall that differences exist in PR isoform ratios between rodent and human tissues. Overall, much remains to be learned about the endogenous genes regulated by progesterone and synthetic progestins in human PR target tissues, and the accuracy of rodents to model human physiology and cancer biology remains to be validated.

IV. COMPOSITION OF PREs

The activity of PR has been extensively studied on 2 exogenous models: the mouse mammary tumor virus-long terminal repeat (MMTV-LTR) and tandem PREs (PRE2) derived from the second PRE of the rat tyrosine amino transferase (TAT) promoter. These sequences, which usually respond to both PR and GR (and often to AR and mineralocorticoid receptors as well), are often referred to as GRE/PREs. It is not surprising that GR and PR recognize the same DNA elements since their core DBDs exhibit 90% amino acid sequence identity (Takimoto *et al*, 2003).

The MMTV-LTR was first demonstrated to be GR regulated and subsequently to be PR regulated. It contains one imperfect palindromic PRE preferentially used by GR, and 3 proximal PRE ½ sites preferentially used by PR (Gowland & Buetti, 1989). Overall, PR occupy a larger DNA footprint (Chalepakis *et al*, 1988) and interact with different nucleotide residues (von der Ahe *et al*, 1985), than do GR. The three PRE ½ sites are necessary for PR induction of MMTV-LTR/luciferase in human T47D cells (Cato *et al*, 1986) and can do so even when isolated from the palindrome (Chalepakis *et al*, 1988; Jacobsen *et al*, 2009). PRB are stronger transactivators than PRA on the complete LTR (Kastner *et al*, 1990) and on the 3 PRE ½ sites (Jacobsen *et al*, 2009). The MMTV-LTR palindrome in combination with 2 of the 3 proximal ½ sites has been used to map the nucleotides that define a PRE using total PR assessed in T47D cells (Lieberman *et al*, 1993). Point mutations demonstrate that even “suboptimal” sequences lead to maximum transcription, but the consensus sequence arrived at consists of 2 hexamer ½ sites separated by 3 intervening bases: 5′-RGnACAnrnTGTnCY-3′. The rat TAT promoter was also first shown to be GR regulated and subsequently to be PR regulated. It contains 3 palindromic PREs, but the PREII alone – 5′-TGTACAggaTGTTCT-3′ – is PR responsive and used in many exogenous promoter/reporters (Strahle *et al*, 1987).

So, what is a GRE/PRE? Depending on which “consensus” sequence is used, the identity varies. Besides the above, two other “consensus” GREs are listed in the TRANSFAC database. One – 5′-GGTACAannTGTYCTk-3′ was derived from 10 sequences, two of which are human: 2 from rat TAT, 2 from rat Tryptophan Oxygenase, 1 from human Metallothionin IIA (MetIIA), 2 from murine Sarcoma Virus, and 1 from human Growth Hormone (Jantzen *et al*, 1987a; Jantzen *et al*, 1987b). Among these 10, a 3′ hexamer (TGTTCT) is more highly conserved than the 5′ hexamer (Jantzen *et al*, 1987a; Jantzen *et al*, 1987b). The second GRE is experimentally derived from 38 GR binding sequences whose identities are unknown. Its sequence is 5′-nnnnnnCnntnTGTNCTnn-3′. It is likely to be the most accurate “PRE”, reflecting true endogenous variability based on functional analyses, including the possibility that a strong PRE ½ site hexamer is sufficient for regulation by PR.

Spacing of PREs, at least in transient transcription assays using synthetic promoters, is reportedly also important for strong PR-mediated transcription. Optimal cooperativity resulting in transcriptional synergism was observed between the imperfect PRE palindrome of MMTV and several transcription factor binding sites including ones for NF1 and SP1 that were 29bp removed from the PRE (Schule *et al*, 1988). A second palindromic PRE also synergizes with the first if the two are separated by 29 nucleotides. It has been suggested that this reflects nucleosome spacing periodicity. However, as reviewed below, it is rare if ever the case that two palindromic PREs are spaced 29nt apart in endogenous promoters; indeed even a single palindromic PRE is hard to find. Cooperative protein-protein interactions resulting in transcriptional synergy have only been observed on MMTV or exogenous PRE-containing reporter constructs in transient transfection assays and only with PRB. PRA do not exhibit synergy under the same conditions, and if co-expressed with PRB,

ER or GR, the PRAs act as transrepressors. However, this may be due to squelching of transcription factors under transient transfection conditions in which the receptors are overexpressed. PRA are not transrepressors of endogenous genes in T47D cells (Graham *et al*, 2005). Also with regard to spacing issues, the distance between a GRE/PRE and the transcription start-site appears to be constrained in experimental models (Nordeen *et al*, 1998), but there is little or no evidence for such rigid position dependence of PREs in natural promoters.

As with MMTV and TAT, many other GR regulated genes are also regulated by liganded PR (Bocquel *et al*, 1989; Renkawitz *et al*, 1984; Slater *et al*, 1988; Vegeto *et al*, 1993), including the chicken *lysozyme*, rabbit *uteroglobin* and human *MetIIA* genes. They have been used to address differences in binding specificities between GR and PR, but often receptors from different species or only one PR isoform were tested. For example, the chicken lysozyme promoter contains 2 palindromic PREs, binding of rat GR and rabbit PRB are the same on the proximal GRE, but PR protect a larger region than GR on the distal GRE, and the two receptors contact different nucleotide residues (von der Ahe *et al*, 1985). In MetIIA, GR and PRB apparently contact the same residues (Slater *et al*, 1988), which, when cloned upstream of the *tk* promoter confer PR inducibility (Scheidereit *et al*, 1986). The uteroglobin promoter, contains 3 PR binding sites between −2732 and −2627 that generate 3 separate footprints (Jantzen *et al*, 1987b), but if they are cloned upstream of a heterologous promoter they fail to confer PR inducibility (Jantzen *et al*, 1987b). PR also bind a site within the first intron of uteroglobin, perhaps explaining the lack of PR activity of the 3 upstream binding sites (Bailly *et al*, 1986). These data demonstrate how complex the issues of PR regulation are, and point to the weaknesses of exogenous promoter analyses. While PR and GR regulate some of the same endogenous genes, they also regulate distinct gene subsets (Wan & Nordeen, 2002). Endogenous binding sites for GR have been mapped by ChIP-chip and ChIP-*seq* (John *et al*, 2011; So *et al*, 2007). However, authentic endogenous binding sites for PR have yet to be mapped by such analyses, and the true identity of PREs and whether or how they differ from GREs, is unknown.

a. Do PR dimers exist?

Biochemical studies and mutational analyses indicate that residues involved in PR dimerization are present in the LBD, DBD and N-terminus of PR monomers (Tetel *et al*, 1997) and it has been assumed that monomers assemble in solution to generate a preformed dimer that binds to DNA with high affinity. Bain *et al.* (Connaghan-Jones *et al*, 2008) have carried out a thermodynamic dissection of PR and conclude that dimer binding at a palindrome (whether by successive monomer assembly or *via* a preformed dimer) is accompanied by an enormous energetic penalty. On the other hand, PR monomers are not only capable of binding DNA but also engage in cooperative interactions among PRE 1/2 -sites of varying distances and orientations, which can account for the majority of the binding energetics on a natural promoter. They conclude that endogenously, PR monomers are the major transcriptionally active species. Our studies, outlined below, indicate that PRE ½-sites may be the major DNA elements through which PR regulate transcription; another argument in favor of a role for monomers.

b. PRE ½ sites and PR monomers

Our i*n silico* analysis of PR-regulated promoters for the presence of PREs shows an abundance of imperfect palindromes, direct repeats and PRE ½ sites. On the other hand, palindromic PREs are rare, and are also detected in promoters of non-PR regulated genes, so that their presence is insufficient to define a PR-regulated promoter (Jacobsen *et al*, 2009). Several lines of evidence suggest that PRE ½ sites may be important PR-regulatory sites: 1) PRE ½ sites are abundant in P-regulated promoters while consensus or perfect palindromes

are rare (Jacobsen *et al*, 2009); 2) transcription can be stimulated by P *via* 2 or 3 PRE ½ sites (Chalepakis *et al*, 1988; Jacobsen *et al*, 2009); 3) PR monomers retain the ability to regulate endogenous genes; indeed mutated PR that are unable to dimerize are better transactivators than wild-type PR (Jacobsen *et al*, 2009); 4) functional studies of endogenous promoters illustrate the recurring theme that liganded PR act *via* PRE ½ sites (Brayman *et al*, 2006; Buser *et al*, 2007; Hewetson & Chilton, 2003; Salama *et al*, 2007); 5) PR bind to PREs as monomers, and monomer binding to the MMTV-LTR ½ sites is cooperative (Connaghan-Jones & Bain, 2009; Connaghan-Jones *et al*, 2008); 6) At molecular protein concentrations found in cells, PR exist as monomers (Connaghan-Jones & Bain, 2009); 7) mobility shift assays using DNA containing PRE ½ sites show PR binding as monomers (Roemer *et al*, 2006). 8) The transcriptional activity of monomeric PR is higher than of dimeric PR on tandem PRE2, possibly due to cooperativity between monomers (Jacobsen *et al*, 2009). Conceptually, these findings may also apply to GR monomers, since mice expressing mutations in the dimerization interface of GR are viable, demonstrating that GR monomers retain the capacity to regulate essential genes (Reichardt *et al*, 1998).

c. Cooperativity, Coregulators and co-Response Elements (coRE)

There is ample evidence that promoter structure confers transcriptional specificity (Maston *et al*, 2006) and the structure and location of PREs relative to adjacent or overlapping DNA binding sites for other transcription factors undoubtedly do so as well. This is the case for the majority of ER binding sites (Carroll *et al*, 2005). Whether PRs, like ERs, require a "pioneer factor" (Carroll *et al*, 2005) that enables their interaction with PREs is unknown. Many sequence-specific DNA binding transcription factors regulated by liganded PR are themselves coregulators of PR-dependent transcription. FOXO1 (Foxo1a) is P-regulated (Ghatge *et al*, 2005) and a coactivator of PRA-dependent transcription (Rudd *et al*, 2007; Takano *et al*, 2007). Other examples include STAT5a (Richer *et al*, 1998), c-Fos (Musgrove *et al*, 1991), c-Jun (Alkhalaf & Murphy, 1992), and CEBPβ (Richer *et al*, 2002), all of which are both P-regulated and capable of interacting with PRE-bound PR. In some cases PREs are not required. Instead, PR are tethered indirectly to DNA-bound factors including AP1 (Bamberger *et al*, 1996; Owen *et al*, 1998) and JDP2 (Hill *et al*, 2009). Occasionally, as is the case for AP1, these are in turn P-regulated (Dai *et al*, 2003). The fact that gene regulation can be preserved with liganded PRs whose DNA binding domain has been mutated supports a tethering model in some cases (Jacobsen and Horwitz, unpublished). With regard to the PR isoforms, our *in silico* analyses show no differences in the PRE composition of PRA *vs*. PRB-regulated promoter (Jacobsen and Horwitz, unpublished) suggesting that the key to PR isoform specificity may lie in the transcription factors that flank PR binding sites, and to differences in binding affinities between these factors and each receptor isoform. While PRA have a higher affinity than PRB for corepressors on an exogenous PRE reporter (Giangrande *et al*, 2000), whether this is the case on endogenous PR binding sites is unknown. These issues will remain unresolved until the structures of the full-length PR isoforms have been solved, and authentic *in vivo* PR binding sites have been identified.

Because we found that imperfect inverted repeats, direct repeats, and PRE ½ sites are widespread in the genome, not only in PR-regulated but also in non-PR-regulated and random promoters, we speculated that PREs may be necessary but not sufficient to control endogenous PR-dependent transcription. A search for PRE partners identified a highly conserved 234-nt sequence invariably located within 1–2 Kb of the transcription start sites of P-regulated genes (Jacobsen *et al*, 2009). It resembles ALU repeats and contains binding sites for 11 transcription factors. Interactions between PR and many of these factors have been documented (Kang *et al*, 2001; Maccarrone *et al*, 2003; Owen *et al*, 1998). We cloned the 234-nt sequence of the PR-regulated *8-oxoguanine DNA glycosylase* promoter in the

forward or reverse orientation in front of 0, 1, or 2 inverted repeat PREs and one or tandem PRE ½-sites driving luciferase. Under these conditions the 234-nt sequence functions as a co-response element (coRE): from the PREs or tandem ½ -sites the reverse coRE is a strong activator of PR and GR-dependent transcription. The forward coRE is a powerful repressor (Jacobsen *et al*, 2009). As discussed above, the prevalence of PRE ½ -sites in natural promoters suggested that PR monomers regulate transcription. Indeed, dimerization-domain mutant PR monomers are stronger transactivators than wild-type PR on PREs or tandem ½ -sites. This is repressed by the forward coRE. We propose that in natural promoters the coRE functions as a composite response element adjacent to imperfect PREs and PRE ½ -sites that presents variable, orientation-dependent transcription factors for cooperative interaction with nearby PR. As discussed below, PR rarely if ever regulate endogenous promoters without the cooperativity provided by coregulatory partners.

V. DETAILED PROMOTER ANALYSES AND PR ISOFORMS

The majority of studies addressing transcriptional mechanisms of PR focus on the proximal promoter (usually 5Kb or less from the 5′-UTR) of the regulated gene, cloned upstream of a reporter, and transfected into cells that contain endogenous or transfected PR. Deletion and/or mutation analysis of the targeted promoter mark PR functional sites, which are then analyzed for presence of “consensus” PRE palindromes, and/or for DNA:PR protein interactions. Often these analyses point to non-consensus PREs or PRE ½ sites, or to other transcription factor binding sites. While these studies are informative, several caveats need to be considered (Table 1): 1) Most studies use chimeric experimental models in which the species of the promoter, the PR, and/or the transfected cells, are heterogenous. Since PRE sequences and sequences for other transcription factors, PR amino acid composition, and cellular factors, differ from species to species, the problems with data interpretation are obvious. 2) Transiently transfected proximal promoters lack the complexity of higher order chromatin structure, and generally lack important regulatory regions found in introns, the 3′ UTR, or thousands of Kb removed from the transcription start-site. All of these sites, distant from proximal promoters, are involved in regulation by ER, AR and GR (Carroll *et al*, 2005; John *et al*, 2011; Lin *et al*, 2009) and are likely to be involved in PR-dependent transcription as well. 3) The origin of PR is important. Endogenous PR activate transcription driven by the MMTV-LTR in the context of chromatin, while transiently expressed PR fail to do so (Botos *et al*, 2004). 4) Many studies use the pGL3/luc vector for promoter construction. This vector is studded with transcription factor binding sites including 46 GRE ½-sites, as well as a palindromic GRE (Dougherty & Sanders, 2005) that would be expected to be PR responsive irrespective of the promoter cloned therein (see below).

We outline below examples of genes believed to be PR-regulated in an isoform-specific manner (Table 1). The mechanism(s) of PR isoform-specific gene regulation remain largely a mystery, however. By expression profiling, some genes appear to be differentially regulated by PRA and others by PRB. Since the two isoforms probably differ structurally (Bain *et al*, 2000; Bain *et al*, 2001) mechanisms for these differences could include unequal DNA sequence binding recognition or affinities, and disparate interactions with coregulatory transcription factors. *In silico* analysis of putative PREs within promoters of genes uniquely regulated by PRA *vs.* PRB do not differ substantially, however (Jacobsen and Horwitz, unpublished).

a. Promoters regulated by both PR (or PRA versus PRB not examined)

Promoter regulation by PR invariably involves interactions with coregulators that differ from gene to gene and sometimes species to species. Undoubtedly these differences are responsible in part, not only for regulatory differences between the PR isoforms, but also

between PR and the other steroid receptors that also require “PREs”, and between the same genes in different species or cells.

Endogenous *FK506 binding protein 5* (FKBP5) is regulated by liganded PR in T47D cells (Hubler *et al*, 2003) through sequences contained within intron E (Hubler & Scammell, 2004). PRB are stronger transactivators than PRA (Richer *et al*, 2002). In mice, FKBP5 regulation requires concomitant binding of PR and GATA-2 also at an intronic sequence (Magklara & Smith, 2009) but it is not known if the two proteins interact or if GATA-2 is required for the human promoter. It is thought that PR bound to intronic DNA causes it to loop back to interact with the proximal promoter.

The human *BCL2-like1* (Bclxl) gene is more strongly regulated by PRA than by PRB in T47D cells (Richer *et al*, 2002). The mouse Bclxl P4 promoter (one of multiple promoters in mice) is also regulated by PR when transfected into T47D cells, but the isoform specificity, if any, is unknown. However, the same promoter is PRB-regulated in HC11 mouse mammary epithelial cells and in COS7 monkey kidney cells. It is postulated, but has not been demonstrated that PR regulation of the mouse promoter involves 2 imperfect PREs that resemble PRE ½ sites (Viegas *et al*, 2004) with GATA3 as a coregulator (Proietti *et al*, 2011).

In T47D cells, *cyclin-dependent kinase inhibitor 1A* (p21) is regulated by both PRA and PRB (Richer *et al*, 2002), with coregulation by SP1 (Owen *et al*, 1998), STAT5a (Richer *et al*, 1998) and STAT3 (Proietti *et al*, 2011). The v-myc myelocytomatosis viral oncogene homolog (avian) (MYC) gene which is rapidly induced by P, contains an imperfect PRE in its promoter that binds PRA and PRB (Moore *et al*, 1997). Interestingly, overexpression of the breast cancer susceptibility BRCA1 protein blocks PR binding to this PRE and increases corepressor recruitment, while knockdown of BRCA1 enhances coactivator recruitment (Katiyar *et al*, 2009). The human NAD+-dependent 15-hydroxyprostaglandin dehydrogenase (PGDH) promoter is regulated by P together with Ets, AP1 and TF. A 2.3 Kb promoter fragment contains 6 PRE ½ sites. Both PR isoforms are functional but PRA regulation is stronger than PRB (Greenland *et al*, 2000) unless PRB effects are enhanced by cAMP signaling, in which case PRB effects exceed PRA (Greenland *et al*, 2000; Sartorius *et al*, 1994a). The ADAM metallopeptidase with thrombospondin type 1 motif (ADAMTS-1) lacks a PRE but is nevertheless PRA and PRB-regulated. It is postulated that regulation occurs through multiple tethering factors including CEBPβ, NF1- like factor, and 3 SP1 sites (Doyle *et al*, 2004). PR also require SP1 to activate the human *glycodelin* promoter (Gao *et al*, 2001) but SP1 does not work on the baboon glycodelin promoter (Jaffe *et al*, 2003).

b. Promoters regulated more strongly or only by PRB

There are many examples of genes and promoters more strongly regulated by PRB. The *breast cancer resistance protein* (BCRP) promoter is P-induced by PRB but not PRA in human placental choriocarcinoma cells (Wang *et al*, 2008), and PRA repress PRB when the two are co-expressed implicating the heterodimer. The proximal 100 nt BCRP promoter contains a “novel PRE” to which both PRA and PRB bind by mobility shift assay. This suggests a dominant negative effect of PRA within the heterodimer as previously reported (Mohamed *et al*, 1994). Similarly, the *mucin 1, cell surface associated* (MUC1) promoter is stimulated by PRB in human uterine epithelial cells, which is antagonized by PRA (Brayman *et al*, 2006). Two PRE ½ sites partially mediate this response, but interactions with other transcription factors are also likely since mutation of the PRE ½ sites does not completely abolish P effects. There is a STAT5 binding site in the promoter that is not involved in regulation of MUC1 in HEC-1A endometrial cancer cells (Brayman *et al*, 2006). Interestingly, PRA represses an ERα-mediated increase of MUC1.

Tissue factor (F3) is strongly regulated by PRB in breast cancer cells (Richer *et al*, 2002) and by total PR in HESC human endometrial stromal cells (Krikun *et al*, 2000) *via* 3 SP1 sites in the proximal promoter. Similarly, the mouse *prostaglandin E2 receptor subtype EP2* promoter is more strongly activated by PRB than PRA through 3 regions that include a novel PR binding sequence and two SP1 binding sites (Tsuchiya *et al*, 2003). The SWI/SNF-related matrix-associated actin-dependent regulator of chromatin-3 **(**RUSH/SMARC3) promoter is regulated by PRB in uterine epithelial cell lines through a PRE ½ site immediately adjacent to a Y-box. PRB mediated regulation is conferred by a chromatin looping mechanism similar to that observed for FKBP5 (Hewetson & Chilton, 2003). The *follicle stimulating hormone, beta polypeptide* (FSHB) promoter is regulated by PRB through 3 PRE-like sequences resembling ½-sites that bind PRA and PRB (O'Conner *et al*, 1997). PRB downregulate the *gonadotropin releasing hormone* (GnRH) promoter *via* non-consensus PREs that also resemble a series of ½ sites (Kepa *et al*, 1996). PRA function was not examined in the latter two studies.

There is significant crosstalk between prolactin (PRL) and P in the mouse mammary gland, with many of the same genes regulated by both hormones, possibly coregulated by STAT5 (Fernandez-Valdivia *et al*, 2008; Goldhar *et al*, 2011; Hilton *et al*). In human breast cancer cells both liganded and unliganded PRs upregulate *PRL receptors* (PRLR) (Jacobsen *et al*, 2002; Tseng & Zhu, 1998). The PRLR promoter lacks a consensus PRE but contains multiple transcription factor binding sites including ones for CEBPβ, SP1 and AP1 (Hu *et al*, 1998) all of which interact with PR (Goldhar *et al*, 2011). In normal mouse epithelial cells, P regulate *inhibitor of differentiation 4* (ID4) via PRB. Its promoter contains 8 putative PRE ½ sites but ChIP studies show PR recruitment to only two of these. Upon PRL treatment, STAT5a also binds this promoter at STAT5 responsive element (S5RE) (Fernandez-Valdivia *et al*, 2008) and co-treatment with PRL and P bring both STAT5a and PR to the promoter. The *human hydroxysteroid (11-beta) dehydrogenase 2* (HSD11B2) gene is more strongly regulated by PRB than PRA (Richer *et al*, 2002); an effect that again involves STAT5a (Subtil-Rodriguez *et al*, 2008). Two mechanisms operate: 1) direct binding of PR to the proximal HSD11B2 promoter; and 2) recruitment of PR to the distal promoter *via* STAT5a. Indeed, STAT5a is an important coregulator of both PRA and PRB activity on many genes. This can be shown by Janus Kinase inhibition, which prevents STAT5 phosphorylation and in turn inhibits P-induction of genes including DUSP1, IL6st, Jun, HMGB3 and STAT5a itself (Subtil-Rodriguez *et al*, 2008).

E74-like factor 5 (ets domain transcription factor) (ELF5), is regulated by recruitment of PR to a binding site within the 4th intron. A putative second PR binding site has been identified 30Kb upstream of the transcription start-site (Hilton *et al*). Liganded PR downregulate expression of *ERα* in breast cancer cells (Ghatge *et al*, 2005) via a PRE ½ site in the ERα promoter (De Amicis *et al*, 2009). ERα downregulation appears to be PRB-specific.

c. Genes regulated more strongly or only by PRA

The *β–casein* promoter is induced by PRL and suppressed more strongly by PRA than PRB (Buser *et al*, 2007). Two PRE ½ sites flank a STAT5a response element in the promoter and P ligands recruit both PR and STAT5 to these sites. Although PRs bind both PRE ½ sites, their affinity and function are stronger on the 5′-site. Both human and mouse PR were tested in this model, with human PRA stronger inhibitors than mouse PR. The human *insulin-like growth factor binding protein 1* (IGFBP1) proximal promoter contains two PREs that are more strongly upregulated by PRA than PRB in endometrial stromal cells. Co-expression of PRB suppresses PRA (Gao *et al*, 2000). Interestingly, HOX proteins suppress (Gao *et al*, 2002) and Foxoa1 increase PR-dependent induction of IGFBP1 *via* either PR isoform (Kim *et al*, 2005).

Liganded PRA regulate the mouse *multidrug resistance 1b* (MDR1b) promoter (Piekarz *et al*, 1993) in T47D cells. The P-responsive region is in the first untranslated exon of the gene, which contains a partial PRE. However PR do not bind there; instead regulation by PR involves CEBPβ and NF-Y (Mallick & Horwitz, 1997). Similarly, the *fibronectin* promoter, which is regulated more strongly by PRA than PRB, lacks a PRE; instead PRA function *via* AP1 and SP1 sites (Tseng *et al*, 2003). Liganded human PRA more strongly regulate the chicken *ovalbumin* promoter than PRB in chicken embryonic fibroblasts (Kastner *et al*, 1990). Similarly, the rat *tyrosine amino transferase* (TAT) promoter is activated more strongly by PRA than PRB in HeLa human cervicocarcinoma cells, but PRB are not dominant negative inhibitors (Vegeto *et al*, 1993). However, PRs do not stimulate the TAT promoter in monkey kidney CV-1 cells; and both PRs stimulate it equally well in human hepatocellular carcinoma HepG2 cells. This emphasizes the importance of controlling the tissue and species specificity of reagents in such studies.

d. PRA and PRB have opposite effects

Kruppel like factor-9 (KLF9) and PR interact to regulate MMTV, cyclin D1 and uteroferrin expression. The *uteroferrin* promoter contains two PRE-like ½ sites (Lamian *et al*, 1993; Zhang *et al*, 2003) at which KLF9 interacts with liganded PRB to superactivate transcription. KLF9 does not modify PRA-dependent transcription, but it enhances repressive effects of PRA without physically interacting with the receptors (Zhang *et al*, 2003). Both PRA and PRB activate the *decidual prolactin* (dPRL) promoter in human endometrial stromal cells. The promoter lacks a palindromic PRE but contains a PRE ½ site and a CEBPβ binding site. Both PR isoforms interact with the inhibitor (LIP) and activator (LAP) isoforms of CEBPβ *in vitro* but only PRA activates dPRL transcription *in vivo* (Christian *et al*, 2002). The *catechol-O-methyltransferase* (COMT) gene has two promoters; one regulates the soluble form of the protein, the other regulates the plasma membrane form. Transcription of COMT is upregulated by PRA and downregulated by PRB, mediated by 3 PRE ½ sites (Salama *et al*, 2007). In human choriocarcinoma placental cells, the human *gonadotropin releasing hormone receptor* (GnRHR) gene is downregulated by PRA and upregulated by PRB, which bind to a nonconsensus PRE (Cheng *et al*, 2001). Similarly, *corticotrophin-releasing hormone* (CRH) promoter expression is decreased by PRA and increased by PRB; in this case mediated by a cAMP regulatory element (Ni *et al*, 2004).

VI. SUMMARY

Progesterone is a key physiologic hormone of women and its receptors play a major role in the diagnosis and treatment of breast cancers. Nevertheless its fundamental mechanisms of action remain in doubt. The receptor proteins have not been purified, crystallographic structural data are unavailable, virtually nothing is known about authentic DNA binding sites on promoters of PR regulated genes, and very little about the true nature of PR interactions with native chromatin. As we review here, in all likelihood, the classical view of PR as dimeric transcription factors that bind a palindromic hormone response element is likely to be either oversimplified or incorrect, given strong evidence that PR function as monomers and that the promoters of PR responsive genes are studded with “half-site” elements. Cumulative data point to cooperative interactions between PR monomers and neighboring coregulatory proteins to bestow progestin specificity to transcriptional responses. A great deal of work has focused on the two PR subunits. Expression profiling data indicate that PRA and PRB regulate different gene subsets suggesting that the two receptors subserve different functions. But, as we point out here, these conclusions are at best preliminary because the models used to perform most studies are problematical. The objective of this review is not meant to highlight these deficiencies and gaps in our knowledge. Rather, we hope to inspire investigators to study these interesting and important receptors using contemporary molecular tools.

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REFERENCES

Abdel-Hafiz H, Takimoto GS, Tung L, Horwitz KB. The inhibitory function in human progesterone receptor N termini binds SUMO-1 protein to regulate autoinhibition and transrepression. J Biol Chem. 2002; 277:33950–6. [PubMed: 12114521]

Alexander IE, Clarke CL, Shine J, Sutherland RL. Progestin inhibition of progesterone receptor gene expression in human breast cancer cells. Mol Endocrinol. 1989; 3:1377–86. [PubMed: 2608065]

Alkhalaf M, Murphy LC. Regulation of c-jun and jun-B by progestins in T-47D human breast cancer cells. Mol Endocrinol. 1992; 6:1625–33. [PubMed: 1448115]

Arnett-Mansfield RL, Graham JD, Hanson AR, Mote PA, Gompel A, Scurr LL, Gava N, de Fazio A, Clarke CL. Focal subnuclear distribution of progesterone receptor is ligand dependent and associated with transcriptional activity. Mol Endocrinol. 2007; 21:14–29. [PubMed: 17021053]

Aupperlee MD, Drolet AA, Durairaj S, Wang W, Schwartz RC, Haslam SZ. Strain-specific differences in the mechanisms of progesterone regulation of murine mammary gland development. Endocrinology. 2009; 150:1485–94. [PubMed: 18988671]

Aupperlee MD, Haslam SZ. Differential hormonal regulation and function of progesterone receptor isoforms in normal adult mouse mammary gland. Endocrinology. 2007; 148:2290–300. [PubMed: 17317767]

Aupperlee MD, Smith KT, Kariagina A, Haslam SZ. Progesterone receptor isoforms A and B: temporal and spatial differences in expression during murine mammary gland development. Endocrinology. 2005; 146:3577–88. [PubMed: 15878961]

Bailly A, Le Page C, Rauch M, Milgrom E. Sequence-specific DNA binding of the progesterone receptor to the uteroglobin gene: effects of hormone, antihormone and receptor phosphorylation. EMBO J. 1986; 5:3235–41. [PubMed: 3816760]

Bain DL, Franden MA, McManaman JL, Takimoto GS, Horwitz KB. The N-terminal region of the human progesterone A-receptor. Structural analysis and the influence of the DNA binding domain. J Biol Chem. 2000; 275:7313–20. [PubMed: 10702302]

Bain DL, Franden MA, McManaman JL, Takimoto GS, Horwitz KB. The N-terminal region of human progesterone B-receptors: biophysical and biochemical comparison to A-receptors. J Biol Chem. 2001; 276:23825–31. [PubMed: 11328821]

Bamberger AM, Bamberger CM, Gellersen B, Schulte HM. Modulation of AP-1 activity by the human progesterone receptor in endometrial adenocarcinoma cells. Proc Natl Acad Sci U S A. 1996; 93:6169–74. [PubMed: 8650238]

Bocquel MT, Kumar V, Stricker C, Chambon P, Gronemeyer H. The contribution of the N- and C-terminal regions of steroid receptors to activation of transcription is both receptor and cell-specific. Nucleic Acids Res. 1989; 17:2581–95. [PubMed: 2717402]

Boney-Montoya J, Ziegler YS, Curtis CD, Montoya JA, Nardulli AM. Long-range transcriptional control of progesterone receptor gene expression. Mol Endocrinol. 2010; 24:346–58. [PubMed: 19952285]

Boonyaratanakornkit V, Scott MP, Ribon V, Sherman L, Anderson SM, Maller JL, Miller WT, Edwards DP. Progesterone receptor contains a proline-rich motif that directly interacts with SH3 domains and activates c-Src family tyrosine kinases. Mol Cell. 2001; 8:269–80. [PubMed: 11545730]

Boonyaratanakornkit V, Strong DD, Mohan S, Baylink DJ, Beck CA, Linkhart TA. Progesterone stimulation of human insulin-like growth factor-binding protein-5 gene transcription in human osteoblasts is mediated by a CACCC sequence in the proximal promoter. J Biol Chem. 1999; 274:26431–8. [PubMed: 10473602]

Botos J, Xian W, Smith DF, Smith CL. Progesterone receptor deficient in chromatin binding has an altered cellular state. J Biol Chem. 2004; 279:15231–9. [PubMed: 14744870]

Bray JD, Jelinsky S, Ghatge R, Bray JA, Tunkey C, Saraf K, Jacobsen BM, Richer JK, Brown EL, Winneker RC, Horwitz KB, Lyttle CR. Quantitative analysis of gene regulation by seven clinically relevant progestins suggests a highly similar mechanism of action through progesterone receptors in T47D breast cancer cells. J Steroid Biochem Mol Biol. 2005; 97:328–41. [PubMed: 16157482]

Brayman MJ, Julian J, Mulac-Jericevic B, Conneely OM, Edwards DP, Carson DD. Progesterone receptor isoforms A and B differentially regulate MUC1 expression in uterine epithelial cells. Mol Endocrinol. 2006; 20:2278–91. [PubMed: 16740655]

Buser AC, Gass-Handel EK, Wyszomierski SL, Doppler W, Leonhardt SA, Schaack J, Rosen JM, Watkin H, Anderson SM, Edwards DP. Progesterone receptor repression of prolactin/signal transducer and activator of transcription 5-mediated transcription of the beta-casein gene in mammary epithelial cells. Mol Endocrinol. 2007; 21:106–25. [PubMed: 16973758]

Carroll JS, Liu XS, Brodsky AS, Li W, Meyer CA, Szary AJ, Eeckhoute J, Shao W, Hestermann EV, Geistlinger TR, Fox EA, Silver PA, Brown M. Chromosome-wide mapping of estrogen receptor binding reveals long-range regulation requiring the forkhead protein FoxA1. Cell. 2005; 122:33–43. [PubMed: 16009131]

Cato AC, Miksicek R, Schutz G, Arnemann J, Beato M. The hormone regulatory element of mouse mammary tumour virus mediates progesterone induction. EMBO J. 1986; 5:2237–40. [PubMed: 3023063]

Chalepakis G, Arnemann J, Slater E, Bruller HJ, Gross B, Beato M. Differential gene activation by glucocorticoids and progestins through the hormone regulatory element of mouse mammary tumor virus. Cell. 1988; 53:371–82. [PubMed: 2835167]

Cheng KW, Cheng CK, Leung PC. Differential role of PR-A and -B isoforms in transcription regulation of human GnRH receptor gene. Mol Endocrinol. 2001; 15:2078–92. [PubMed: 11731610]

Cho H, Aronica SM, Katzenellenbogen BS. Regulation of progesterone receptor gene expression in MCF-7 breast cancer cells: a comparison of the effects of cyclic adenosine 3′,5′-monophosphate, estradiol, insulin-like growth factor-I, and serum factors. Endocrinology. 1994; 134:658–64. [PubMed: 7507831]

Christian M, Pohnke Y, Kempf R, Gellersen B, Brosens JJ. Functional association of PR and CCAAT/enhancer-binding protein beta isoforms: promoter-dependent cooperation between PR-B and liver-enriched inhibitory protein, or liver-enriched activatory protein and PR-A in human endometrial stromal cells. Mol Endocrinol. 2002; 16:141–54. [PubMed: 11773445]

Cicatiello L, Addeo R, Sasso A, Altucci L, Petrizzi VB, Borgo R, Cancemi M, Caporali S, Caristi S, Scafoglio C, Teti D, Bresciani F, Perillo B, Weisz A. Estrogens and progesterone promote persistent CCND1 gene activation during G1 by inducing transcriptional derepression via c-Jun/c-Fos/estrogen receptor (progesterone receptor) complex assembly to a distal regulatory element and recruitment of cyclin D1 to its own gene promoter. Mol Cell Biol. 2004; 24:7260–74. [PubMed: 15282324]

Clarke CL, Graham J, Roman SD, Sutherland RL. Direct transcriptional regulation of the progesterone receptor by retinoic acid diminishes progestin responsiveness in the breast cancer cell line T-47D. J Biol Chem. 1991; 266:18969–75. [PubMed: 1918012]

Clarke CL, Roman SD, Graham J, Koga M, Sutherland RL. Progesterone receptor regulation by retinoic acid in the human breast cancer cell line T-47D. J Biol Chem. 1990; 265:12694–700. [PubMed: 2373707]

Clemens JW, Robker RL, Kraus WL, Katzenellenbogen BS, Richards JS. Hormone induction of progesterone receptor (PR) messenger ribonucleic acid and activation of PR promoter regions in ovarian granulosa cells: evidence for a role of cyclic adenosine 3′,5′-monophosphate but not estradiol. Mol Endocrinol. 1998; 12:1201–14. [PubMed: 9717846]

Condon JC, Hardy DB, Kovaric K, Mendelson CR. Up-regulation of the progesterone receptor (PR)-C isoform in laboring myometrium by activation of nuclear factor-kappaB may contribute to the onset of labor through inhibition of PR function. Mol Endocrinol. 2006; 20:764–75. [PubMed: 16339279]

Connaghan-Jones KD, Bain DL. Using thermodynamics to understand progesterone receptor function: method and theory. Methods Enzymol. 2009; 455:41–70. [PubMed: 19289202]

Connaghan-Jones KD, Heneghan AF, Miura MT, Bain DL. Thermodynamic dissection of progesterone receptor interactions at the mouse mammary tumor virus promoter: monomer binding and strong cooperativity dominate the assembly reaction. J Mol Biol. 2008; 377:1144–60. [PubMed: 18313072]

Cui X, Lazard Z, Zhang P, Hopp TA, Lee AV. Progesterone crosstalks with insulin-like growth factor signaling in breast cancer cells via induction of insulin receptor substrate-2. Oncogene. 2003a; 22:6937–41. [PubMed: 14534541]

Cui X, Zhang P, Deng W, Oesterreich S, Lu Y, Mills GB, Lee AV. Insulin-like growth factor-I inhibits progesterone receptor expression in breast cancer cells via the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin pathway: progesterone receptor as a potential indicator of growth factor activity in breast cancer. Mol Endocrinol. 2003b; 17:575–88. [PubMed: 12554765]

Dai D, Litman ES, Schonteich E, Leslie KK. Progesterone regulation of activating protein-1 transcriptional activity: a possible mechanism of progesterone inhibition of endometrial cancer cell growth. J Steroid Biochem Mol Biol. 2003; 87:123–31. [PubMed: 14672732]

Daniel AR, Gaviglio AL, Czaplicki LM, Hillard CJ, Housa D, Lange CA. The progesterone receptor hinge region regulates the kinetics of transcriptional responses through acetylation, phosphorylation, and nuclear retention. Mol Endocrinol. 2010; 24:2126–38. [PubMed: 20861224]

Daniel AR, Knutson TP, Lange CA. Signaling inputs to progesterone receptor gene regulation and promoter selectivity. Mol Cell Endocrinol. 2009; 308:47–52. [PubMed: 19549591]

De Amicis F, Zupo S, Panno ML, Malivindi R, Giordano F, Barone I, Mauro L, Fuqua SA, Ando S. Progesterone receptor B recruits a repressor complex to a half-PRE site of the estrogen receptor alpha gene promoter. Mol Endocrinol. 2009; 23:454–65. [PubMed: 19147702]

Dougherty DC, Sanders MM. Comparison of the responsiveness of the pGL3 and pGL4 luciferase reporter vectors to steroid hormones. Biotechniques. 2005; 39:203–7. [PubMed: 16116793]

Doyle KM, Russell DL, Sriraman V, Richards JS. Coordinate transcription of the ADAMTS-1 gene by luteinizing hormone and progesterone receptor. Mol Endocrinol. 2004; 18:2463–78. [PubMed: 15256533]

Eeckhoute J, Keeton EK, Lupien M, Krum SA, Carroll JS, Brown M. Positive cross-regulatory loop ties GATA-3 to estrogen receptor alpha expression in breast cancer. Cancer Res. 2007; 67:6477–83. [PubMed: 17616709]

Fernandez-Valdivia R, Mukherjee A, Creighton CJ, Buser AC, DeMayo FJ, Edwards DP, Lydon JP. Transcriptional response of the murine mammary gland to acute progesterone exposure. Endocrinology. 2008; 149:6236–50. [PubMed: 18687774]

Gao J, Mazella J, Seppala M, Tseng L. Ligand activated hPR modulates the glycodelin promoter activity through the Sp1 sites in human endometrial adenocarcinoma cells. Mol Cell Endocrinol. 2001; 176:97–102. [PubMed: 11369448]

Gao J, Mazella J, Tang M, Tseng L. Ligand-activated progesterone receptor isoform hPR-A is a stronger transactivator than hPR-B for the expression of IGFBP-1 (insulin-like growth factor binding protein-1) in human endometrial stromal cells. Mol Endocrinol. 2000; 14:1954–61. [PubMed: 11117526]

Gao J, Mazella J, Tseng L. Hox proteins activate the IGFBP-1 promoter and suppress the function of hPR in human endometrial cells. DNA Cell Biol. 2002; 21:819–25. [PubMed: 12489992]

Ghatge RP, Jacobsen BM, Schittone SA, Horwitz KB. The progestational and androgenic properties of medroxyprogesterone acetate: gene regulatory overlap with dihydrotestosterone in breast cancer cells. Breast Cancer Res. 2005; 7:R1036–50. [PubMed: 16457685]

Giangrande PH, Kimbrel EA, Edwards DP, McDonnell DP. The opposing transcriptional activities of the two isoforms of the human progesterone receptor are due to differential cofactor binding. Mol Cell Biol. 2000; 20:3102–15. [PubMed: 10757795]

Goldhar AS, Duan R, Ginsburg E, Vonderhaar BK. Progesterone induces expression of the prolactin receptor gene through cooperative action of Sp1 and C/EBP. Mol Cell Endocrinol. 2011; 335:148–57. [PubMed: 21238538]

Gowland PL, Buetti E. Mutations in the hormone regulatory element of mouse mammary tumor virus differentially affect the response to progestins, androgens, and glucocorticoids. Mol Cell Biol. 1989; 9:3999–4008. [PubMed: 2550809]

Graham JD, Clarke CL. Physiological action of progesterone in target tissues. Endocr Rev. 1997; 18:502–19. [PubMed: 9267762]

Graham JD, Mote PA, Salagame U, van Dijk JH, Balleine RL, Huschtscha LI, Reddel RR, Clarke CL. DNA replication licensing and progenitor numbers are increased by progesterone in normal human breast. Endocrinology. 2009; 150:3318–26. [PubMed: 19342456]

Graham JD, Roman SD, McGowan E, Sutherland RL, Clarke CL. Preferential stimulation of human progesterone receptor B expression by estrogen in T-47D human breast cancer cells. J Biol Chem. 1995a; 270:30693–700. [PubMed: 8530508]

Graham JD, Yager ML, Hill HD, Byth K, O'Neill GM, Clarke CL. Altered progesterone receptor isoform expression remodels progestin responsiveness of breast cancer cells. Mol Endocrinol. 2005; 19:2713–35. [PubMed: 15976005]

Graham JD, Yeates C, Balleine RL, Harvey SS, Milliken JS, Bilous AM, Clarke CL. Characterization of progesterone receptor A and B expression in human breast cancer. Cancer Res. 1995b; 55:5063–8. [PubMed: 7585552]

Greenland KJ, Jantke I, Jenatschke S, Bracken KE, Vinson C, Gellersen B. The human NAD+-dependent 15-hydroxyprostaglandin dehydrogenase gene promoter is controlled by Ets and activating protein-1 transcription factors and progesterone. Endocrinology. 2000; 141:581–97. [PubMed: 10650939]

Groshong SD, Owen GI, Grimison B, Schauer IE, Todd MC, Langan TA, Sclafani RA, Lange CA, Horwitz KB. Biphasic regulation of breast cancer cell growth by progesterone: role of the cyclin-dependent kinase inhibitors, p21 and p27(Kip1). Mol Endocrinol. 1997; 11:1593–607. [PubMed: 9328342]

Hewetson A, Chilton BS. An Sp1-NF-Y/progesterone receptor DNA binding-dependent mechanism regulates progesterone-induced transcriptional activation of the rabbit RUSH/SMARCA3 gene. J Biol Chem. 2003; 278:40177–85. [PubMed: 12890680]

Hill KK, Roemer SC, Jones DN, Churchill ME, Edwards DP. A progesterone receptor co-activator (JDP2) mediates activity through interaction with residues in the carboxyl-terminal extension of the DNA binding domain. J Biol Chem. 2009; 284:24415–24. [PubMed: 19553667]

Hilton HN, Kalyuga M, Cowley MJ, Alles MC, Lee HJ, Caldon CE, Blazek K, Kaplan W, Musgrove EA, Daly RJ, Naylor MJ, Graham JD, Clarke CL, Ormandy CJ. The antiproliferative effects of progestins in T47D breast cancer cells are tempered by progestin induction of the ETS transcription factor Elf5. Mol Endocrinol. 2010; 24:1380–92. [PubMed: 20519331]

Hopp TA, Weiss HL, Hilsenbeck SG, Cui Y, Allred DC, Horwitz KB, Fuqua SA. Breast cancer patients with progesterone receptor PR-A-rich tumors have poorer disease-free survival rates. Clin Cancer Res. 2004; 10:2751–60. [PubMed: 15102680]

Horwitz KB, Koseki Y, McGuire WL. Estrogen control of progesterone receptor in human breast cancer: role of estradiol and antiestrogen. Endocrinology. 1978; 103:1742–51. [PubMed: 748014]

Hovland AR, Powell RL, Takimoto GS, Tung L, Horwitz KB. An N-terminal inhibitory function, IF, suppresses transcription by the A-isoform but not the B-isoform of human progesterone receptors. J Biol Chem. 1998; 273:5455–60. [PubMed: 9488667]

Hu ZZ, Zhuang L, Meng J, Dufau ML. Transcriptional regulation of the generic promoter III of the rat prolactin receptor gene by C/EBPbeta and Sp1. J Biol Chem. 1998; 273:26225–35. [PubMed: 9748306]

Hubler TR, Denny WB, Valentine DL, Cheung-Flynn J, Smith DF, Scammell JG. The FK506-binding immunophilin FKBP51 is transcriptionally regulated by progestin and attenuates progestin responsiveness. Endocrinology. 2003; 144:2380–7. [PubMed: 12746298]

Hubler TR, Scammell JG. Intronic hormone response elements mediate regulation of FKBP5 by progestins and glucocorticoids. Cell Stress Chaperones. 2004; 9:243–52. [PubMed: 15544162]

Huggins GS, Wong JY, Hankinson SE, De Vivo I. GATA5 activation of the progesterone receptor gene promoter in breast cancer cells is influenced by the +331G/A polymorphism. Cancer Res. 2006; 66:1384–90. [PubMed: 16452193]

Ilenchuk TT, Walters MR. Rat uterine progesterone receptor analyzed by [3H]R5020 photoaffinity labeling: evidence that the A and B subunits are not equimolar. Endocrinology. 1987; 120:1449–56. [PubMed: 3030701]

Ismail PM, Li J, DeMayo FJ, O'Malley BW, Lydon JP. A novel LacZ reporter mouse reveals complex regulation of the progesterone receptor promoter during mammary gland development. Mol Endocrinol. 2002; 16:2475–89. [PubMed: 12403837]

Jacobsen BM, Jambal P, Schittone SA, Horwitz KB. ALU repeats in promoters are position-dependent co-response elements (coRE) that enhance or repress transcription by dimeric and monomeric progesterone receptors. Mol Endocrinol. 2009; 23:989–1000. [PubMed: 19372234]

Jacobsen BM, Richer JK, Schittone SA, Horwitz KB. New human breast cancer cells to study progesterone receptor isoform ratio effects and ligand-independent gene regulation. J Biol Chem. 2002; 277:27793–800. [PubMed: 12021276]

Jacobsen BM, Schittone SA, Richer JK, Horwitz KB. Progesterone-independent effects of human progesterone receptors (PRs) in estrogen receptor-positive breast cancer: PR isoform-specific gene regulation and tumor biology. Mol Endocrinol. 2005; 19:574–87. [PubMed: 15563544]

Jaffe RC, Donnelly KM, Fazleabas AT. The induction of baboon glycodelin expression by progesterone is not through Sp1. Mol Hum Reprod. 2003; 9:35–40. [PubMed: 12529418]

Jantzen HM, Strahle U, Gloss B, Stewart F, Schmid W, Boshart M, Miksicek R, Schutz G. Cooperativity of glucocorticoid response elements located far upstream of the tyrosine aminotransferase gene. Cell. 1987a; 49:29–38. [PubMed: 2881624]

Jantzen K, Fritton HP, Igo-Kemenes T, Espel E, Janich S, Cato AC, Mugele K, Beato M. Partial overlapping of binding sequences for steroid hormone receptors and DNaseI hypersensitive sites in the rabbit uteroglobin gene region. Nucleic Acids Res. 1987b; 15:4535–52. [PubMed: 3453115]

John S, Sabo PJ, Thurman RE, Sung MH, Biddie SC, Johnson TA, Hager GL, Stamatoyannopoulos JA. Chromatin accessibility pre-determines glucocorticoid receptor binding patterns. Nat Genet. 2011; 43:264–8. [PubMed: 21258342]

Kang HY, Lin HK, Hu YC, Yeh S, Huang KE, Chang C. From transforming growth factor-beta signaling to androgen action: identification of Smad3 as an androgen receptor coregulator in prostate cancer cells. Proc Natl Acad Sci U S A. 2001; 98:3018–23. [PubMed: 11248024]

Kariagina A, Aupperlee MD, Haslam SZ. Progesterone receptor isoforms and proliferation in the rat mammary gland during development. Endocrinology. 2007; 148:2723–36. [PubMed: 17332059]

Kastner P, Krust A, Turcotte B, Stropp U, Tora L, Gronemeyer H, Chambon P. Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. EMBO J. 1990; 9:1603–14. [PubMed: 2328727]

Katiyar P, Ma Y, Riegel A, Fan S, Rosen EM. Mechanism of BRCA1-mediated inhibition of progesterone receptor transcriptional activity. Mol Endocrinol. 2009; 23:1135–46. [PubMed: 19389812]

Kepa JK, Jacobsen BM, Boen EA, Prendergast P, Edwards DP, Takimoto G, Wierman ME. Direct binding of progesterone receptor to nonconsensus DNA sequences represses rat GnRH. Mol Cell Endocrinol. 1996; 117:27–39. [PubMed: 8734471]

Kim JJ, Buzzio OL, Li S, Lu Z. Role of FOXO1A in the regulation of insulin-like growth factor-binding protein-1 in human endometrial cells: interaction with progesterone receptor. Biol Reprod. 2005; 73:833–9. [PubMed: 15987820]

Kraus WL, Montano MM, Katzenellenbogen BS. Cloning of the rat progesterone receptor gene 5′-region and identification of two functionally distinct promoters. Mol Endocrinol. 1993; 7:1603–16. [PubMed: 8145766]

Kraus WL, Montano MM, Katzenellenbogen BS. Identification of multiple, widely spaced estrogen-responsive regions in the rat progesterone receptor gene. Mol Endocrinol. 1994; 8:952–69. [PubMed: 7997237]

Krikun G, Schatz F, Mackman N, Guller S, Demopoulos R, Lockwood CJ. Regulation of tissue factor gene expression in human endometrium by transcription factors Sp1 and Sp3. Mol Endocrinol. 2000; 14:393–400. [PubMed: 10707957]

Lamian V, Gonzalez BY, Michel FJ, Simmen RC. Non-consensus progesterone response elements mediate the progesterone-regulated endometrial expression of the uteroferrin gene. J Steroid Biochem Mol Biol. 1993; 46:439–50. [PubMed: 8217875]

Lange CA, Richer JK, Shen T, Horwitz KB. Convergence of progesterone and epidermal growth factor signaling in breast cancer. Potentiation of mitogen-activated protein kinase pathways. J Biol Chem. 1998; 273:31308–16. [PubMed: 9813039]

Lange CA, Shen T, Horwitz KB. Phosphorylation of human progesterone receptors at serine-294 by mitogen-activated protein kinase signals their degradation by the 26S proteasome. Proc Natl Acad Sci U S A. 2000; 97:1032–7. [PubMed: 10655479]

Leo JC, Wang SM, Guo CH, Aw SE, Zhao Y, Li JM, Hui KM, Lin VC. Gene regulation profile reveals consistent anticancer properties of progesterone in hormone-independent breast cancer cells transfected with progesterone receptor. Int J Cancer. 2005; 117:561–8. [PubMed: 15945099]

Lieberman BA, Bona BJ, Edwards DP, Nordeen SK. The constitution of a progesterone response element. Mol Endocrinol. 1993; 7:515–27. [PubMed: 8388996]

Lin B, Wang J, Hong X, Yan X, Hwang D, Cho JH, Yi D, Utleg AG, Fang X, Schones DE, Zhao K, Omenn GS, Hood L. Integrated expression profiling and ChIP-seq analyses of the growth inhibition response program of the androgen receptor. PLoS One. 2009; 4:e6589. [PubMed: 19668381]

Maccarrone M, Bari M, Di Rienzo M, Finazzi-Agro A, Rossi A. Progesterone activates fatty acid amide hydrolase (FAAH) promoter in human T lymphocytes through the transcription factor Ikaros. Evidence for a synergistic effect of leptin. J Biol Chem. 2003; 278:32726–32. [PubMed: 12799380]

Magklara A, Smith CL. A composite intronic element directs dynamic binding of the progesterone receptor and GATA-2. Mol Endocrinol. 2009; 23:61–73. [PubMed: 19036901]

Mallick S, Horwitz SB. Transcriptional regulation of the murine multidrug resistance gene mdr1b by progesterone occurs via an indirect mechanism. DNA Cell Biol. 1997; 16:807–18. [PubMed: 9260924]

Maston GA, Evans SK, Green MR. Transcriptional regulatory elements in the human genome. Annu Rev Genomics Hum Genet. 2006; 7:29–59. [PubMed: 16719718]

McGowan EM, Clarke CL. Effect of overexpression of progesterone receptor A on endogenous progestin-sensitive endpoints in breast cancer cells. Mol Endocrinol. 1999; 13:1657–71. [PubMed: 10517668]

Mohamed MK, Tung L, Takimoto GS, Horwitz KB. The leucine zippers of c-fos and c-jun for progesterone receptor dimerization: A-dominance in the A/B heterodimer. J Steroid Biochem Mol Biol. 1994; 51:241–50. [PubMed: 7826885]

Moore MR, Zhou JL, Blankenship KA, Strobl JS, Edwards DP, Gentry RN. A sequence in the 5′ flanking region confers progestin responsiveness on the human c-myc gene. J Steroid Biochem Mol Biol. 1997; 62:243–52. [PubMed: 9408078]

Mote PA, Bartow S, Tran N, Clarke CL. Loss of co-ordinate expression of progesterone receptors A and B is an early event in breast carcinogenesis. Breast Cancer Res Treat. 2002; 72:163–72. [PubMed: 12038707]

Mote PA, Graham JD, Clarke CL. Progesterone receptor isoforms in normal and malignant breast. Ernst Schering Found Symp Proc. 2007:77–107. [PubMed: 18540569]

Musgrove EA, Lee CS, Sutherland RL. Progestins both stimulate and inhibit breast cancer cell cycle progression while increasing expression of transforming growth factor alpha, epidermal growth factor receptor, c-fos, and c-myc genes. Mol Cell Biol. 1991; 11:5032–43. [PubMed: 1922031]

Ni X, Hou Y, Yang R, Tang X, Smith R, Nicholson RC. Progesterone receptors A and B differentially modulate corticotropin-releasing hormone gene expression through a cAMP regulatory element. Cell Mol Life Sci. 2004; 61:1114–22. [PubMed: 15112058]

Nishida K, Kitazawa R, Mizuno K, Maeda S, Kitazawa S. Identification of regulatory elements of human alpha 6 integrin subunit gene. Biochem Biophys Res Commun. 1997; 241:258–63. [PubMed: 9425259]

Nordeen SK, Ogden CA, Taraseviciene L, Lieberman BA. Extreme position dependence of a canonical hormone response element. Mol Endocrinol. 1998; 12:891–8. [PubMed: 9626664]

O'Conner JL, Wade MF, Prendergast P, Edwards DP, Boonyaratanakornkit V, Mahesh VB. A 361 base pair region of the rat FSH-beta promoter contains multiple progesterone receptor-binding

sequences and confers progesterone responsiveness. Mol Cell Endocrinol. 1997; 136:67–78. [PubMed: 9510069]

Owen GI, Richer JK, Tung L, Takimoto G, Horwitz KB. Progesterone regulates transcription of the p21(WAF1) cyclin-dependent kinase inhibitor gene through Sp1 and CBP/p300. J Biol Chem. 1998; 273:10696–701. [PubMed: 9553133]

Park-Sarge OK, Mayo KE. Regulation of the progesterone receptor gene by gonadotropins and cyclic adenosine 3′,5′-monophosphate in rat granulosa cells. Endocrinology. 1994; 134:709–18. [PubMed: 8299566]

Petz LN, Ziegler YS, Loven MA, Nardulli AM. Estrogen receptor alpha and activating protein-1 mediate estrogen responsiveness of the progesterone receptor gene in MCF-7 breast cancer cells. Endocrinology. 2002; 143:4583–91. [PubMed: 12446585]

Petz LN, Ziegler YS, Schultz JR, Kim H, Kemper JK, Nardulli AM. Differential regulation of the human progesterone receptor gene through an estrogen response element half site and Sp1 sites. J Steroid Biochem Mol Biol. 2004a; 88:113–22. [PubMed: 15084343]

Petz LN, Ziegler YS, Schultz JR, Nardulli AM. Fos and Jun inhibit estrogen-induced transcription of the human progesterone receptor gene through an activator protein-1 site. Mol Endocrinol. 2004b; 18:521–32. [PubMed: 14684847]

Piekarz RL, Cohen D, Horwitz SB. Progesterone regulates the murine multidrug resistance mdr1b gene. J Biol Chem. 1993; 268:7613–6. [PubMed: 8096515]

Proietti CJ, Beguelin W, Flaque MC, Cayrol F, Rivas MA, Tkach M, Charreau EH, Schillaci R, Elizalde PV. Novel role of signal transducer and activator of transcription 3 as a progesterone receptor coactivator in breast cancer. Steroids. 2011; 76:381–92. [PubMed: 21184768]

Purmonen S, Manninen T, Pennanen P, Ylikomi T. Progestins regulate genes that can elicit both proliferative and antiproliferative effects in breast cancer cells. Oncol Rep. 2008; 19:1627–34. [PubMed: 18497975]

Reichardt HM, Kaestner KH, Tuckermann J, Kretz O, Wessely O, Bock R, Gass P, Schmid W, Herrlich P, Angel P, Schutz G. DNA binding of the glucocorticoid receptor is not essential for survival. Cell. 1998; 93:531–41. [PubMed: 9604929]

Renkawitz R, Schutz G, von der Ahe D, Beato M. Sequences in the promoter region of the chicken lysozyme gene required for steroid regulation and receptor binding. Cell. 1984; 37:503–10. [PubMed: 6722881]

Richer JK, Jacobsen BM, Manning NG, Abel MG, Wolf DM, Horwitz KB. Differential gene regulation by the two progesterone receptor isoforms in human breast cancer cells. J Biol Chem. 2002; 277:5209–18. [PubMed: 11717311]

Richer JK, Lange CA, Manning NG, Owen G, Powell R, Horwitz KB. Convergence of progesterone with growth factor and cytokine signaling in breast cancer. Progesterone receptors regulate signal transducers and activators of transcription expression and activity. J Biol Chem. 1998; 273:31317–26. [PubMed: 9813040]

Roemer SC, Donham DC, Sherman L, Pon VH, Edwards DP, Churchill ME. Structure of the progesterone receptor-deoxyribonucleic acid complex: novel interactions required for binding to half-site response elements. Mol Endocrinol. 2006; 20:3042–52. [PubMed: 16931575]

Rudd MD, Gonzalez-Robayna I, Hernandez-Gonzalez I, Weigel NL, Bingman WE 3rd, Richards JS. Constitutively active FOXO1a and a DNA-binding domain mutant exhibit distinct co-regulatory functions to enhance progesterone receptor A activity. J Mol Endocrinol. 2007; 38:673–90. [PubMed: 17556536]

Salama SA, Jamaluddin M, Kumar R, Hassan MH, Al-Hendy A. Progesterone regulates catechol-O-methyl transferase gene expression in breast cancer cells: distinct effect of progesterone receptor isoforms. J Steroid Biochem Mol Biol. 2007; 107:253–61. [PubMed: 17689241]

Salih SM, Salama SA, Jamaluddin M, Fadl AA, Blok LJ, Burger CW, Nagamani M, Al-Hendy A. Progesterone-mediated regulation of catechol-O-methyl transferase expression in endometrial cancer cells. Reprod Sci. 2008; 15:210–20. [PubMed: 18089588]

Santos SJ, Aupperlee MD, Xie J, Durairaj S, Miksicek R, Conrad SE, Leipprandt JR, Tan YS, Schwartz RC, Haslam SZ. Progesterone receptor A-regulated gene expression in mammary organoid cultures. J Steroid Biochem Mol Biol. 2009; 115:161–72. [PubMed: 19383543]

Sartorius CA, Groshong SD, Miller LA, Powell RL, Tung L, Takimoto GS, Horwitz KB. New T47D breast cancer cell lines for the independent study of progesterone B- and A-receptors: only antiprogestin-occupied B-receptors are switched to transcriptional agonists by cAMP. Cancer Res. 1994a; 54:3868–77. [PubMed: 8033109]

Sartorius CA, Melville MY, Hovland AR, Tung L, Takimoto GS, Horwitz KB. A third transactivation function (AF3) of human progesterone receptors located in the unique N-terminal segment of the B-isoform. Mol Endocrinol. 1994b; 8:1347–60. [PubMed: 7854352]

Savouret JF, Bailly A, Misrahi M, Rauch C, Redeuilh G, Chauchereau A, Milgrom E. Characterization of the hormone responsive element involved in the regulation of the progesterone receptor gene. EMBO J. 1991; 10:1875–83. [PubMed: 2050123]

Scheidereit C, Krauter P, von der Ahe D, Janich S, Rabenau O, Cato AC, Suske G, Westphal HM, Beato M. Mechanism of gene regulation by steroid hormones. J Steroid Biochem. 1986; 24:19–24. [PubMed: 3009974]

Schneider W, Ramachandran C, Satyaswaroop PG, Shyamala G. Murine progesterone receptor exists predominantly as the 83-kilodalton ‘A’ form. J Steroid Biochem Mol Biol. 1991; 38:285–91. [PubMed: 2009220]

Schule R, Muller M, Kaltschmidt C, Renkawitz R. Many transcription factors interact synergistically with steroid receptors. Science. 1988; 242:1418–20. [PubMed: 3201230]

Schultz JR, Petz LN, Nardulli AM. Estrogen receptor alpha and Sp1 regulate progesterone receptor gene expression. Mol Cell Endocrinol. 2003; 201:165–75. [PubMed: 12706304]

Seagroves TN, Lydon JP, Hovey RC, Vonderhaar BK, Rosen JM. C/EBPbeta (CCAAT/enhancer binding protein) controls cell fate determination during mammary gland development. Mol Endocrinol. 2000; 14:359–68. [PubMed: 10707954]

Shen T, Horwitz KB, Lange CA. Transcriptional hyperactivity of human progesterone receptors is coupled to their ligand-dependent down-regulation by mitogen-activated protein kinase-dependent phosphorylation of serine 294. Mol Cell Biol. 2001; 21:6122–31. [PubMed: 11509655]

Slater EP, Cato AC, Karin M, Baxter JD, Beato M. Progesterone induction of metallothionein-IIA gene expression. Mol Endocrinol. 1988; 2:485–91. [PubMed: 2843758]

So AY, Chaivorapol C, Bolton EC, Li H, Yamamoto KR. Determinants of cell- and gene-specific transcriptional regulation by the glucocorticoid receptor. PLoS Genet. 2007; 3:e94. [PubMed: 17559307]

Sriraman V, Sharma SC, Richards JS. Transactivation of the progesterone receptor gene in granulosa cells: evidence that Sp1/Sp3 binding sites in the proximal promoter play a key role in luteinizing hormone inducibility. Mol Endocrinol. 2003; 17:436–49. [PubMed: 12554796]

Strahle U, Klock G, Schutz G. A DNA sequence of 15 base pairs is sufficient to mediate both glucocorticoid and progesterone induction of gene expression. Proc Natl Acad Sci U S A. 1987; 84:7871–5. [PubMed: 2891134]

Subtil-Rodriguez A, Millan-Arino L, Quiles I, Ballare C, Beato M, Jordan A. Progesterone induction of the 11beta-hydroxysteroid dehydrogenase type 2 promoter in breast cancer cells involves coordinated recruitment of STAT5A and progesterone receptor to a distal enhancer and polymerase tracking. Mol Cell Biol. 2008; 28:3830–49. [PubMed: 18378698]

Takano M, Lu Z, Goto T, Fusi L, Higham J, Francis J, Withey A, Hardt J, Cloke B, Stavropoulou AV, Ishihara O, Lam EW, Unterman TG, Brosens JJ, Kim JJ. Transcriptional cross talk between the forkhead transcription factor forkhead box O1A and the progesterone receptor coordinates cell cycle regulation and differentiation in human endometrial stromal cells. Mol Endocrinol. 2007; 21:2334–49. [PubMed: 17609436]

Takimoto GS, Tung L, Abdel-Hafiz H, Abel MG, Sartorius CA, Richer JK, Jacobsen BM, Bain DL, Horwitz KB. Functional properties of the N-terminal region of progesterone receptors and their mechanistic relationship to structure. J Steroid Biochem Mol Biol. 2003; 85:209–19. [PubMed: 12943706]

Tetel MJ, Jung S, Carbajo P, Ladtkow T, Skafar DF, Edwards DP. Hinge and amino-terminal sequences contribute to solution dimerization of human progesterone receptor. Mol Endocrinol. 1997; 11:1114–28. [PubMed: 9212059]

Tora L, Gronemeyer H, Turcotte B, Gaub MP, Chambon P. The N-terminal region of the chicken progesterone receptor specifies target gene activation. Nature. 1988; 333:185–8. [PubMed: 2835683]

Tseng L, Tang M, Wang Z, Mazella J. Progesterone receptor (hPR) upregulates the fibronectin promoter activity in human decidual fibroblasts. DNA Cell Biol. 2003; 22:633–40. [PubMed: 14611684]

Tseng L, Zhu HH. Progestin, estrogen, and insulin-like growth factor-I stimulate the prolactin receptor mRNA in human endometrial stromal cells. J Soc Gynecol Investig. 1998; 5:149–55.

Tsuchiya S, Tanaka S, Sugimoto Y, Katsuyama M, Ikegami R, Ichikawa A. Identification and characterization of a novel progesterone receptor-binding element in the mouse prostaglandin E receptor subtype EP2 gene. Genes Cells. 2003; 8:747–58. [PubMed: 12940822]

Tung L, Abdel-Hafiz H, Shen T, Harvell DM, Nitao LK, Richer JK, Sartorius CA, Takimoto GS, Horwitz KB. Progesterone receptors (PR)-B and -A regulate transcription by different mechanisms: AF-3 exerts regulatory control over coactivator binding to PR-B. Mol Endocrinol. 2006; 20:2656–70. [PubMed: 16762974]

Vegeto E, Shahbaz MM, Wen DX, Goldman ME, O'Malley BW, McDonnell DP. Human progesterone receptor A form is a cell- and promoter-specific repressor of human progesterone receptor B function. Mol Endocrinol. 1993; 7:1244–55. [PubMed: 8264658]

Viegas LR, Vicent GP, Baranao JL, Beato M, Pecci A. Steroid hormones induce bcl-X gene expression through direct activation of distal promoter P4. J Biol Chem. 2004; 279:9831–9. [PubMed: 14679196]

Vienonen A, Syvala H, Miettinen S, Tuohimaa P, Ylikomi T. Expression of progesterone receptor isoforms A and B is differentially regulated by estrogen in different breast cancer cell lines. J Steroid Biochem Mol Biol. 2002; 80:307–13. [PubMed: 11948015]

von der Ahe D, Janich S, Scheidereit C, Renkawitz R, Schutz G, Beato M. Glucocorticoid and progesterone receptors bind to the same sites in two hormonally regulated promoters. Nature. 1985; 313:706–9. [PubMed: 2983219]

Wan Y, Nordeen SK. Overlapping but distinct gene regulation profiles by glucocorticoids and progestins in human breast cancer cells. Mol Endocrinol. 2002; 16:1204–14. [PubMed: 12040008]

Wang H, Lee EW, Zhou L, Leung PC, Ross DD, Unadkat JD, Mao Q. Progesterone receptor (PR) isoforms PRA and PRB differentially regulate expression of the breast cancer resistance protein in human placental choriocarcinoma BeWo cells. Mol Pharmacol. 2008; 73:845–54. [PubMed: 18042733]

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. [PubMed: 2082185]

Wei LL, Krett NL, Francis MD, Gordon DF, Wood WM, O'Malley BW, Horwitz KB. Multiple human progesterone receptor messenger ribonucleic acids and their autoregulation by progestin agonists and antagonists in breast cancer cells. Mol Endocrinol. 1988; 2:62–72. [PubMed: 3398843]

Xie Y, Wang YL, Yu L, Hu Q, Ji L, Zhang Y, Liao QP. Metformin promotes progesterone receptor expression via inhibition of mammalian target of rapamycin (mTOR) in endometrial cancer cells. J Steroid Biochem Mol Biol. 2010

Xu X, Murdoch FE, Curran EM, Welshons WV, Fritsch MK. Transcription factor accessibility and histone acetylation of the progesterone receptor gene differs between parental MCF-7 cells and a subline that has lost progesterone receptor expression. Gene. 2004; 328:143–51. [PubMed: 15019994]

Yang C, Chen L, Li C, Lynch MC, Brisken C, Schmidt EV. Cyclin D1 enhances the response to estrogen and progesterone by regulating progesterone receptor expression. Mol Cell Biol. 2010; 30:3111–25. [PubMed: 20404095]

Yie SM, Xiao R, Librach CL. Progesterone regulates HLA-G gene expression through a novel progesterone response element. Hum Reprod. 2006; 21:2538–44. [PubMed: 16684846]

Zhang XL, Zhang D, Michel FJ, Blum JL, Simmen FA, Simmen RC. Selective interactions of Kruppel-like factor 9/basic transcription element-binding protein with progesterone receptor

isoforms A and B determine transcriptional activity of progesterone-responsive genes in endometrial epithelial cells. J Biol Chem. 2003; 278:21474–82. [PubMed: 12672823]

Table 1

Summary of promoters analyzed for regulation by PRA or PRB

Gene Symbol	PRA	PRB	Pattern of regulation PRA/PRB	Species (PR)	Species (promoter)	Species (cells)	PRE^	Reference
Regulated by Total PR								
FAAH	endog	endog	up (total)	human	Human	human; T lymphocytes	None; Ikaros binding site	(Maccarrone *et al*, 2003)
*ITGA6	endog	endog	up (total)	human	Human	human; MCF7	Imperfect palindrome PRE	(Nishida *et al*, 1997)
*FKBP5	endog	endog	up (total)	human	Human	human; T47D	PRE-like sequences	(Hubler & Scammell, 2004)
LYZ	endog	endog	up (total)	chicken	Chicken	chicken; primary oviduct	hexanucleotide (PRE 1/2 site)	(Renkawitz *et al*, 1984)
dPRL	exog	exog	up, up PRB > PRA	human	Human	human; primary endometrial stroma	PRE 1/2 site close to C/EBPβ	(Christian *et al*, 2002)
PRLR	endog	endog	up (total)	human	Mouse	human; T47D	None; AP1, C/EBPβ	(Goldhar *et al*, 2011)
HSD11B2	exog, endog	exog, endog	up, up PRB > PRA	human	Human	human; T47D-YV	Putative HRE and S5RE	(Subtil-Rodriguez *et al*, 2008)
*BCL2L1 (Bclxl)	endog	endog	up (total)	human	Mouse	human; T47D	2 imperfect HREs	(Viegas *et al*, 2004)
MYC	endog	endog	up (total)	human	Human	human; T47D	PRE-like sequence	(Moore *et al*, 1997)
OGG1	exog	exog	up (total)	human	Human	human; HeLa, T47D	None; coRE binds 11 transcription factors	(Jacobsen *et al*, 2009)
CDKN1A (p21)	exog	exog	up (total)	human	Human	human; HeLa (for PRA) T47D-YB	None; SP1 binding site	(Owen *et al*, 1998)
F3	endog	endog	up (total)	human	Human	human; primary endometrial stroma	None; 3 SP1 binding sites	(Krikun *et al*, 2000)
ADAMTS1	exog	exog	up (total)	human	Mouse	rat; granulosa	None; C/EBPβ, NF1 and 3 SP1 sites	(Doyle *et al*, 2004)
PAEP (glycodelin)	endog	endog	up (total)	human	Human	human; HEC-1B	None; SP1 sites	(Gao *et al*, 2001)
HLA-G	endog	endog	up (total)	human	Human	human; JEG3	Novel PRE	(Yie *et al*, 2006)
*COMT	endog	endog	down (total)	human	Human	human; T47D and MCF7	3 PRE 1/2 sites	(Salama *et al*, 2007)
Regulated by PRB only								

Gene Symbol	PRA	PRB	Pattern of regulation PRA/PRB	Species (PR)	Species (promoter)	Species (cells)	PRE^	Reference
or PRB > PRA								
UF (uteroferrin)	exog	exog	nc, up; PRA inhibits PRB	human	Porcine	human and monkey; HEC-1A and COS1	Non-consensus PRE and 2 PRE 1/2 sites	(Lamian *et al*, 1993; Zhang *et al*, 2003)
PTGER2 (prostaglandin E2 receptor)	exog	exog	up, up; PRB > PRA	mouse	mouse	human; HeLa	Novel PR binding sequence (GG/ACCGGA) and SP1	(Tsuchiya *et al*, 2003)
BCRP	exog	exog	up, up; PRA inhibits PRB	human	human	human; BeWo	Novel PRE	(Wang *et al*, 2008)
MUC1	exog	exog	up, up; PRA inhibits PRB	human	human	human; HEC-1A	2 PRE 1/2 sites	(Brayman *et al*, 2006; Gowland & Buetti, 1989)
MMTV	exog	exog	up, up; PRB > PRA	human	virus	human; HeLa, T47D	3 PRE 1/2 sites, 1 imperfect PRE	(Cato *et al*, 1986; Gowland & Buetti, 1989; Kastner *et al*, 1990)
ESR	exog	exog	nc, down	human	human	human; MCF7, ZR75, HeLa	PRE 1/2 site	(De Amicis *et al*, 2009)
FSHB	nd	exog	nd, up	human	rat	rat; primary pituitary	3 PRE-like sequences	(O'Conner *et al*, 1997)
RUSH/SMARC3	nd	endog	nd, up	rabbit	rabbit	rabbit; SV40 transformed uterine epithelial	PRE 1/2 site	(Hewetson & Chilton, 2003)
GNRH1	nd	exog	nd, down	human	rat	mouse; GT1-7 pituitary	Non-consensus PRE	(Kepa *et al*, 1996)
*ITGA6	exog	exog	nc, up	human	human	human; HeLa	Unknown	(Richer *et al*, 2002)
*FKBP5	nd	exog	nd, up	chicken	mouse	mouse; 3017.1 cells and human; T47D, HeLa	composite PRE/GATA2 binding site	(Magklara & Smith, 2009)
Regulated by PRA only or PRA > PRB								
FN1	exog	exog	up, up; PRA>PRB	human	human	human; decidual fibroblasts	none; AP1/CRE and SP1 sites	(Tseng *et al*, 2003)
*BCL2L1 (Bclxl)	exog	exog	up, down	human	human	human; HeLa	unknown	(Richer *et al*, 2002)
SERPINB9 (Ovalbumin)	exog	exog	up, nc	human	chicken	chicken; embryonic fibroblasts	unknown	(Kastner *et al*, 1990)

Gene Symbol	PRA	PRB	Pattern of regulation PRA/PRB	Species (PR)	Species (promoter)	Species (cells)	PRE^	Reference
SERPINB9 (Ovalbumin)	exog	exog	up, up; PRA>PRB	chicken	chicken	chicken; embryonic ibroblasts	unknown	(Tora *et al*, 1988)
IGFBP5	exog	nd	up, nd	human	human	human; U2 osteosarcoma	2 tandem caccc boxes	(Boonyaratanakornkit *et al*, 1999)
TAT	exog	exog	up, PRA>PRB	human	rat	human; HeLa	3 GREs as reported in (Jantzen *et al*, 1987a)	(Vegeto *et al*, 1993)
PGDH	exog	exog	up, up PRA > PRB; +cAMP PRB > PRA	human	human	human; myometrial smooth muscle	unknown; contains 8 PRE 1/2 sites	(Greenland *et al*, 2000)
Abcb1b (mdr1b)	endog, exog	endog, exog	up, nc	human	mouse	human; T47D	unknown	(Piekarz *et al*, 1993)
CSN2 (Beta casein)	exog	exog	PRL up, PRA>PRB down	human	rat	monkey; COS1	2 PRE 1/2 sites; 5′ site > 3′ site	(Buser *et al*, 2007)
IGFBP1	exog	exog	up, up PRA>PRB	human	human	human; endometrial stromal	2 PREs	(Gao *et al*, 2000)
Genes oppositely regulated by PRA and PRB								
*COMT	exog	exog	up, down	human	human	human; Ishikawa endometrial cancer	2 PRE 1/2 sites	(Salih *et al*, 2008)
CRH	exog	exog	down, up	human	human	human; primary placental	cAMP regulatory element	(Ni *et al*, 2004)
GNRHR	endog, exog	endog, exog	down, up	human	human	JEG3 human choriocarcinoma placental	Putative PRE	(Cheng *et al*, 2001)
PR:DNA interactions, no functional data								
ELF5	endog	endog	mRNA up	human	mouse	ChIP in T47D	unknown; 4th Intron	(Hilton *et al*)
ID4	nd	exog	nd, mRNA up mouse PR	human	mouse	mouse; normal mammary epithelial	2 PRE 1/2 sites	(Fernandez-Valdivia *et al*, 2008)
Uteroglobin	nd	endog	nd, mRNA up in endometrium	rabbit	rabbit	in vitro	3 PREs	(Jantzen *et al*, 1987b)

Gene Symbol	PRA	PRB	Pattern of regulation PRA/PRB	Species (PR)	Species (promoter)	Species (cells)	PRE^	Reference
MET IIA	nd	endog	nd, up (heterologous promoter)	rabbit	human	T47D (mRNA)	HRE	(Slater *et al*, 1988)

Table refers to functional studies except where noted

Only genes whose promoter studied listed in table

nd= not done

nc=no change

endog=endogenous

exog= exogenous

*=gene present in more than one category

^=as defined by authors