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Review

# Integration of progesterone receptor action with rapid signaling events in breast cancer models☆

Carol A. Lange *

*University of Minnesota Cancer Center, Departments of Medicine (Division of Hematology, Oncology, and Transplant) and Pharmacology, 420 Delaware Street SE, MMC 806, Minneapolis, MN 55455, United States*

**Abstract**

Recent discoveries suggest that several protein kinases are rapidly activated in response to ligand binding to cytoplasmic steroid hormone receptors (SRs), including progesterone receptors (PRs). Thus, PRs act as ligand-activated transcription factor "sensors" for growth factor-initiated signaling pathways in hormonally regulated tissues, such as the breast. Induction of rapid signaling upon progestin binding to PR-B provides a means to ensure that receptors and co-regulators are appropriately phosphorylated as part of optimal transcription complexes. Alternatively, PR-B activated kinase cascades provide additional avenues for progestin-regulated gene expression independent of PR nuclear action. Herein, an overview of progesterone/PR and signaling cross-talk in breast cancer models is provided. Kinases are emerging as key mediators of PR action. Cross-talk between SR and membrane-initiated signaling events suggests a mechanism for coordinate regulation of gene subsets by mitogenic stimuli in hormonally responsive normal tissues, and is suspected to contribute to cancer biology.


*Keywords:* Progesterone receptor; Epidermal growth factor; Mitogen activated protein kinase; Cyclin D1; Breast cancer; c-Src kinase

## Contents



*Abbreviations:* AF, activation function; AR, androgen receptor; CDK2, cyclin-dependent protein kinase 2; DBD, DNA binding domain; EGF, epidermal growth factor; ER, estrogen receptor; H, hinge; HBD, hormone binding domain; Hsp, heat shock protein; MAPK, p42/p44 mitogen activated protein kinases; MEKK, MAPK/ERK kinase kinase; MEK, MAPK/ERK kinase; MMTV, mouse mammary tumor virus; mPR, membrane progesterone receptor; PR, progesterone receptor; PRE, progesterone response element; SERM, selective estrogen receptor modulator; SH2, Src-homology two domain (interaction with phosphotyrosine residues); SH3, Src-homology three domain (interaction with proline-rich regions); SR, steroid hormone receptor; SRC, steroid receptor coactivator; STAT, signal transducer and activator of transcription; TIFs, transcription intermediary factors; TRAPs, thyroid receptor-associated proteins (known as DRIPs, vitamin D receptor-interacting proteins).

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* Tel.: +1 612 626 0621; fax: +1 612 626 4915.
*E-mail address:* Lange047@umn.edu.

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## 1. Introduction

The underlying molecular mechanisms of uncontrolled cellular proliferation, survival, and maintenance of breast cancer phenotypes are poorly understood. However, it is clear that dysregulation of estrogen and/or progesterone receptor action contributes to the development and progression of a majority of breast cancers. Steroid hormones and their cognate steroid receptors (SRs) exert direct effects in the nucleus as transcription factors. In addition, SRs function at the membrane and/or in the cytosol as mediators of growth factor-initiated signaling pathways. Recent observations indicate that membrane-associated SRs rapidly activate cytoplasmic signaling pathways as an alternative route for regulating SR-induced nuclear transcriptional events. This independent avenue for coordinating gene regulation occurs by the activation of cytoplasmic kinase pathways and independently of direct SR nuclear action. Recently, progestins have been recognized as mediators of increased post-menopausal breast cancer risk when taken as part of combined hormone replacement therapy relative to estrogen alone or placebo [1]. This review will examine PR-initiated genomic and nongenomic signaling pathways in breast cancer models with the purpose of identifying key kinases involved in two branches of one integrated pathway. Integration of rapid cytoplasmic signaling events with PR nuclear actions has important implications for breast cancer progression.

## 2. Classical actions of PRs

PRs are activated through binding with the ovarian steroid ligand, progesterone. PRs are classically defined as ligand-activated transcription factors that regulate gene expression by binding directly or indirectly to DNA. Three PR isoforms are the product of a single gene located on chromosome 11 at q22–23 that undergoes transcription via the use of alternate promoters and internal translational start sites [2]. PR isoforms consist of the full length PR-B (116 kDa), N-terminally truncated PR-A (94 kDa), and PR-C isoforms (60 kDa). PR-positive cells usually co-express PR-A and PR-B isoforms; these receptors have different transcriptional activities within the same promoter context, but can also recognize entirely different promoters [3,4]. PR-B is required for normal mammary gland development [5], while PR-A is essential for uterine development and reproductive function [6]. PR-C is devoid of classical transcriptional activity, and instead functions as a dominant inhibitor of uterine PR-B in the fundal myometrium during labor [7]. In the absence of progesterone, PRs are complexed with several chaperone molecules including heat shock protein (hsp) 90, hsp70, hsp40, Hop and, p23; these interactions are requisite for proper protein folding and assembly of stable PR–hsp90 heterocomplexes that are competent to bind ligand [8]. Hsps also function to connect PRs to protein trafficking systems. After binding to progesterone, the receptors undergo restructuring, dimerization, and hsp dissociation. Activated receptors bind directly to specific progesterone response elements (PREs) and PRE-like sequences in the promoter regions of such target genes as c-myc [9], fatty acid synthetase [10], and MMTV [11]. Treatment with progestin also results in an upregulation of regulatory molecules without classical PREs in their proximal promoter regions, such as epidermal growth factor receptor [12,13], c-fos [14,15], and cyclin D1 [16,17]. Without canonical PREs, PR regulation of these genes can occur through indirect DNA binding mechanisms, as in the example of PR binding to specificity protein 1 to promote p21 transcription in the presence of progestin [18]. PRs may also regulate genes by tethering to activating protein 1 [19] or signal transducers and activators of transcription (STATs) [15,20].

When either directly or indirectly bound to DNA, PRs regulate the basal transcription machinery in conjunction with nuclear receptor coregulatory molecules. Coregulators modulate transcription through chromatin remodeling and recruitment of transcriptional machinery (e.g., RNA polymerase-II). Histone acetyl transferases (HATs) and histone deacetylases (HDACS) function as coactivators and corepressors, respectively. Both HATs and HDACS coordinate transcriptional activity with other regulator proteins, including the ATP-dependent chromatin remodeling complexes (SWI/SNF), arginine methyltransferases (CARM1 and PRMT1), and histone kinases (reviewed in [21]).

## 3. PR and signaling cross-talk in breast cancer

Normal breast development requires ERα PRs, and growth factors. Estrogen stimulates ductal elongation, and progestins induce ductal sidebranching and alveologenesis [22]. Epidermal growth factor (EGF), in addition to promoting the proliferation of terminal end-buds, augments estrogen-induced ductal outgrowth and progesterone-induced sidebranching [23]. Indeed, estrogen induces PR isoform expression only in the presence of EGF [24], suggesting the existence of important cross-talk between EGFRs and both SRs. Ligand-activated PRs and ERs are potent breast mitogens, and mammary epithelial cells that express PR also express ERα. Moreover, estrogen is usually required in order to induce the expression of PR. For these reasons, separating the effects of progesterone alone from estrogen have been difficult. Consequently, the direct role of PR isoforms in breast cancer remains poorly defined relative to the role of ERα in breast development and breast cancer.

PR and ER are expressed by a minority of non-dividing epithelial cells in the lumen of the mature mammary gland. PR- and ER-positive cells constitute only ∼7–10% of the epithelial cell population in the normal adult mammary gland. This non-proliferative condition appears to be sustained by such inhibitory molecules as TGF-beta or high levels of p27, the CDK inhibitor (reviewed in [25]). In response to communication between stromal and epithe-