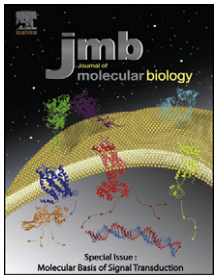
Review



Progesterone Receptor Signaling Mechanisms

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Abstract

Progesterone receptor (PR) is a master regulator in female reproductive tissues that controls developmental processes and proliferation and differentiation during the reproductive cycle and pregnancy. PR also plays a role in progression of endocrine-dependent breast cancer. As a member of the nuclear receptor family of ligand-dependent transcription factors, the main action of PR is to regulate networks of target gene expression in response to binding its cognate steroid hormone, progesterone. This paper summarizes recent advances in understanding the structure–function properties of the receptor protein and the tissue/cell-type-specific PR signaling pathways that contribute to the biological actions of progesterone in the normal breast and in breast cancer.

Introduction

Progesterone receptor (PR) is a member of the nuclear/steroid hormone receptor (SHR) family of ligand-dependent transcription factors that is expressed primarily in female reproductive tissues and in the central nervous system. In response to binding its cognate steroid hormone, progesterone, PR regulates the expression of gene networks to control development, differentiation, and proliferation of target tissues and the pathological processes in endocrine-based cancers [1]. The variability of the biological actions of progesterone is context dependent, involving factors such as the tissue/cell-type- and developmental-stage-specific availability of PR-interacting co-regulatory proteins (CoRs) and other cooperating transcription factors, the accessibility of target genes to interact with PR within the chromatin landscape, and the cell-type-specific protein signaling pathways that serve either as inputs to regulate PR activity or as downstream effectors of PR and target genes [2–5]. Another source of functional diversity is the highly dynamic conformational flexibility of SHR structures [6,7]. Although there are common features and mechanisms for all SHR and other members of the nuclear receptor family, this review summarizes recent advances in areas defining unique PR signaling mechanisms that explain the actions of progesterone and focuses on the normal mammary gland and breast cancer.

Dynamic Structures of PR

In common with other SHRs, PR is a modular protein composed of a well-folded C-terminal ligand-binding domain (LBD), a central globular DNA-binding domain (DBD), and an amino-terminal domain (NTD) that is composed largely of intrinsically disordered (ID) protein. There are two PR protein isoforms that arise from the same gene by utilization of two promoters: PR-A with a truncated NTD and full-length PR-B (Fig. 1). PR contains two transcriptional activation domains or "functions" (AFs) that provide interaction surfaces for CoRs; AF1 is located within the NTD and AF2 is in the LBD [6,8,9]. High-resolution X-ray crystallography structures of individual DBD and LBD have provided substantial insights into how PR and other steroid receptors recognize and bind hormone response element DNA of target genes and how the LBD acts as an allosteric control switch in response to binding hormone. Hormonal ligands induce conformational changes in LBD helices (most notably helix 12) to

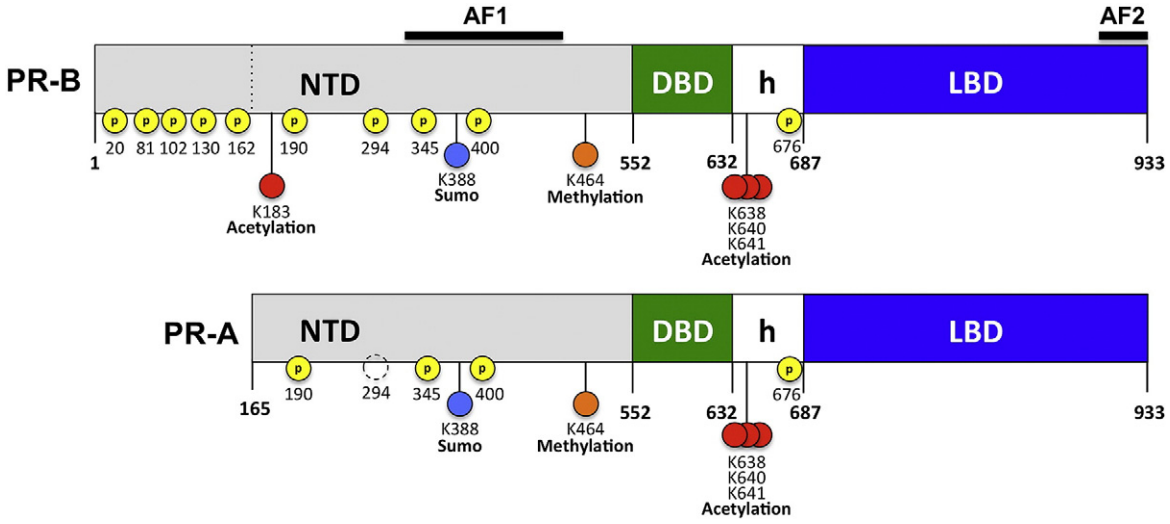

Fig. 1. Structural domains of human PR and post-translational modifications. Ligand-binding domain (LBD), DNA-binding domain (DBD), amino-terminal domain (NTD), transcriptional activation or functional domains (AF1, AF2), and phosphorylated serine residues (p).

form an AF2 pocket that binds to structural motifs within CoRs that serve as mediators of transcriptional activation or repression [10–13]. No high-resolution structures have been reported for the NTD or for any intact, full-length nuclear receptor; thus, little is known about the molecular basis by which CoRs regulate AF1 activity. This is despite the fact that AF1 is just as functionally important as AF2 in mediated transcriptional activity of SHR [14,15]. Even with the absence of high-resolution structures of an intact, full-length SHR, an emerging picture from other experimental approaches is that the full spectrum of SHR activity requires functional synergy between AF1 and AF2 involving allosteric interdomain interactions and dynamic conformational flexibility of the NTD [7,9,16–18]. As examples, DNA can act as an allosteric regulator affecting the binding of CoRs to AF2 or NTD/AF1 surfaces [19–24], and the NTD can allosterically transmit unfolding within the DBD or LBD [25]. The short hinge region between LBD and DBD of PR is also ID and is a binding site for other proteins including Jun dimerization protein 2. Jun dimerization protein 2 binding enhanced the transcriptional activity of AF1 at a distance through stabilizing secondary structure and tertiary folding of the NTD [6,21,23]. Although SHR domains can function independently, they affect each other's activity and structural conformations when linked together in the intact receptor [7,19,26,27].

ID regions of regulatory proteins have become increasingly appreciated to play important roles in molecular recognition and in mediating signaling responses [28–30]. ID polypeptides exist as dynamic conformational ensembles and can carry out functions by a “coupled folding and binding” process where binding with a partner protein or DNA induces the ID region to undergo a disorder-to-order transition [31,32]. This flexibility and process appear to have certain advantages for intra- and intermolecular interactions as compared with that of ordered structural motifs. For example, ID polypeptides have larger, extended surfaces for interaction with a much wider range of CoRs and thus have the potential to form an array of functional conformations. This mechanism creates the opportunity for the same ID region to respond to a variety of signals. The “coupled folding and binding” process also results in high-specificity and low affinity binding, which are ideal properties for transient, reversible interactions of transcription factors with other proteins [28–32]. Solution biophysical methods have been used to directly demonstrate that the NTDs of all SHRs, including PR, are largely composed of ID conformations deficient in stable secondary structures. The NTD of PR and other steroid receptors has also been shown to undergo folding into a more stable secondary and tertiary structure upon binding to other proteins, such as the general transcription factor TATA binding protein (TBP) [15,33–37]. TBP was also observed to be associated with the enhancement of NTD/AF1 transcriptional activity by a mechanism whereby TBP-induced folding facilitated the binding of steroid receptor coactivator 1 and enhanced the steroid receptor coactivator 1-dependent, AF1-mediated transcriptional activity [15,33,37]. Thus, TBP has been proposed to act by reorganizing structures in the NTD required for recognition and assembly of coactivator complexes. The fact that TBP interaction has similar effects on the NTD of other SHRs, despite the poorly conserved sequences of the NTDs, suggests a common mechanism of action of NTD/AF1s.

Hydrogen–deuterium exchange (HDX) coupled with mass spectrometry (MS) has emerged as a powerful