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At the Cutting Edge

Epigenetic regulation of Progesterone Receptor isoforms: From classical models to the sexual brain

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ABSTRACT

Progesterone Receptor is a member of the nuclear receptor superfamily, which regulates several functions in both reproductive and non-reproductive tissues. Progesterone Receptor gene encodes for two main isoforms, A and B, and contains two specific promoters with their respective transcription start sites. The mRNA expression of both isoforms is mainly regulated by estrogens and specifically via the Estrogen Receptor Alpha, in a context specific manner. Furthermore, it has been reported in extensive physiological and pathological models that Progesterone Receptor isoforms regulation is related to the epigenetic state of their respective promoters. Epigenetic regulation of Progesterone Receptor isoforms in the brain is a recent and scarcely explored field in neurosciences. This review focuses on the epigenetic mechanisms involved in Progesterone Receptor regulation, emphasizing the implications for the sexual brain. Future directions for research about this important field are also discussed.

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Abbreviations: 3C, chromosome conformation capture; 5hmC, 5 hydroxymethylcytosine; Ago, Argonaute; AP1, Activator Protein 1; AZA, aza-2′-deoxycytidine; ChIP, chromatin immunoprecipitation; DHSS, Dnase I hypersensitive sites; DNMT, DNA methyl transferases; ERE, estrogen responsive elements; eRNA, enhancer RNA; ERα, Estrogen Receptor Alpha; H, histone; H3Ac, acetylated histone 3; H3K27me3, histone 3 trimethylated at lysine 27; H3K4me, histone 3 methylated at lysine 4; H3K4me, histone 3 methylated at lysine 4; H3K4me1, histone 3 monomethylated at lysine 4; H3K4me3, histone 3 trimethylated at lysine 4; H3K9Ac, histone 3 acetylated at lysine 9; H3K9me2, histone 3 dimethylated at lysine 9; H3K9me3, histone 3 trimethylated at lysine 9; H3R2me2a, histone 3 dimethylated at arginine 4 (asymmetric); H4Ac, acetylated histone 4; HATs, histone acetyl transferases; HDACs, histone deacetylases; JARID1A, Jumonji AT-rich interactive domain 1A; lNCRNA, long non-coding RNA; MBH, mediobasal hypothalamus; miRNA, microRNA; MLL1, Myeloid Lymphoid or mixed lineage Leukemia; POA, preoptic area; PPRA, Progesterone Receptor isoform A promoter; PPRB, Progesterone Receptor isoform B promoter; PR, Progesterone Receptor; PRA, Progesterone Receptor isoform A; PRB, Progesterone Receptor isoform B; pri-miRNAs, primary miRNA transcripts; RISC, RNA-induced silencing complex; SB, sodium butyrate; SET1A, SET domain containing 1A; siRNA, small interfering RNA; SMYD3, SET and MYND domain-containing protein 3; SRC, Steroid Receptor Coactivator; SP1, Specific Protein 1; TSA, trichostatin A; UTR, Untranslated region; VMH, ventromedial nucleus of hypothalamus; VPA, valproic acid.

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0. Introduction

Steroid hormone nuclear receptors are transcription factors that regulate proliferation, growth and differentiation, as well as many other functions in several mammalian tissues. Progesterone Receptor (PR) belongs to the steroid receptor superfamily (O'Malley et al., 1970). *PR* gene expresses two main isoforms, *PRA* and *PRB*, which are regulated by two different promoters and transcription start sites (Kraus et al., 1993). *PRB* differs from *PRA* by having additional 164 amino acids at the amino terminus of the protein. Both isoforms have different functions that are mediated by specific molecular mechanisms of gene regulation (Vegeto et al., 1993). In fact, *PRA* usually functions as a transcriptional inhibitor of *PRB* gene targets. Moreover, it has been reported that both isoforms act as transcriptional activators of different genes in the same cell (Richer et al., 2002). This means that the physiological activity of PR is the result of the counterbalancing proportion of these isoforms when both are present in the same cells (Camacho-Arroyo et al., 2007; Guerra-Araiza et al., 2000). Indeed, our group and others have shown that there is a specific variation in PR isoforms throughout the estrous cycle and with hormonal treatments in the rodent brain. Interestingly, this pattern of variation has been associated with the onset of sexual behavior (Camacho-Arroyo et al., 1998; Guerra-Araiza et al., 2003; White et al., 2007; Mendoza-Garcés et al., 2010, 2013).

The main regulator of the balance between *PR* gene isoforms is the Estrogen Receptor Alpha (ERα), which carries out this function via interaction with its specific ligand, despite the lack of consensus estrogen responsive elements (ERE) in the *PR* gene isoforms promoter regions (Kastner et al., 1990). It has been reported that ERα is recruited to the *PR* gene promoter through interactions with Specific Protein 1 (SP1) and Activator Protein-1 (AP1) in MCF7 cells (Petz et al., 2002, 2004). However, recent studies on the same cell line suggest that ERα is associated at distal regulatory regions of the *PR* gene after short times of estradiol exposure, rather than acting on the promoter region (Boney-Montoya et al., 2010; Won Jeong et al., 2012). In addition, ligand bound ERα recruits transcriptional coregulators that are dependent on the specific gene, regulatory region, time and cellular context (Won Jeong et al., 2012). These coregulators, in turn, induce changes in chromatin in order to activate transcription. The induction of the *PR* gene isoforms also depends on the DNA methylation and chromatin basal state of their promoters (Fleury et al., 2008).

This suggests a complex mechanism of *PR* gene regulation that involves the participation of epigenetic processes. In fact, it has been reported extensively in physiological and pathological models that *PR* gene regulation involves promoter epigenetic changes. Here we summarize the main findings regarding the epigenetic regulation of PR, emphasizing and discussing the recent advances in the field of neurosciences.

1. Epigenetic regulation of *PR* gene isoforms

Epigenetics is classically defined as the study of stable heritable changes in gene function that are not the result of modifications of the DNA sequence (Dupont et al., 2009). However, due to the increasing knowledge of molecular mechanisms involved in this field, this definition is now considered limited (Felsenfeld, 2014). Epigenetic regulation of gene expression involves posttranslational modifications of histones, DNA methylation, noncoding RNAs, and long range interactions, among other events. The former two have been extensively studied in many pathological processes (such as cancer), as they are potentially reversible and therefore represent a promising target for therapeutics (Biçaku et al., 2008; Hansberg-Pastor et al., 2013; Ren et al., 2007; Walton et al., 2008). However, the differential expression of *PRB* and *PRA* isoforms in different physiological and pathological situations, particularly in non-reproductive tissues such as the brain, cannot be fully explained by the available information about the epigenetic regulation of PR isoform promoters.

1.1. Histone modifications

Chromatin is defined as a compact nuclear structure that contains the genomic DNA. The fundamental unit of chromatin is the nucleosome, which is integrated by a histones octamer that is composed of four dimers of each histone (H2A, H2B, H3 and H4) and is wrapped into approximately 146 bp DNA (Luger et al., 1997). Nucleosomes are connected to each other by histone H1 and linker DNA. The histone tails contain residues that are targets of posttranslational modifications, such as acetylation, methylation and phosphorylation (Jenuwein and Allis, 2001).

Acetylation takes place as result of the enzymatic activities of histone acetyl transferases (HATs) that promote transcription (Lander et al., 2001; Oñate et al., 1995), and histone deacetylases (HDACs) that exert the opposite effect. In general terms, the effect of the other histone modifications depends on the particular residue that is being targeted as well as the combinatorial modifications in other residues and/or histones (Kouzarides, 2007).

These posttranslational modifications are made by specific coregulators, which are recruited by nuclear receptors after binding to their cognate DNA response elements on target genes. This in turn results in the formation of an active or repressive transcriptional complex that directs transcription (McKenna et al., 1999; Glass and Rosenfeld, 2000). Moreover, the requirement of specific coregulators depends on the nuclear receptor, tissue and regulated gene. For example, the induction of the *PR* gene in rodent brain requires mainly Steroid Receptor Coactivators 1 and 2 (SRC1 and SRC2), unlike MFC7 cells that only require SRC3 (Apostolakis et al., 2002; Molenda et al., 2002; Won Jeong et al., 2012). In addition, another layer of complexity results from the fact that some coregulators could function as coactivators or corepressors, depending on the cellular and gene context (Carling et al., 2004; Peterson et al., 2007; Catchpole et al., 2011; Won Jeong et al., 2012). Since there are comprehensive reviews of the function and regulation of nuclear receptor coregulators (Tetel et al., 2009; Tognoni et al., 2011; Tetel and Acharya, 2013), this section will focus particularly on the histone marks. First, we will describe the participation of histone modifications in classical models (Sections 1.1.1–1.1.3) and then focus on the sexual brain (Section 2.1).