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PROGESTERONE RECEPTORS AND Sp/KRÜPPEL-LIKE FAMILY MEMBERS IN THE UTERINE ENDOMETRIUM

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TABLE OF CONTENTS

1. ABSTRACT

Sp/KLF family members, of which at least 20 distinct nuclear proteins are known to date, serve as transcription factors by binding to GC-enriched sites within target gene promoters. These molecules regulate diverse cellular processes such as proliferation, differentiation, and apoptosis, via their interactions with various other nuclear proteins in promoter- and cell-context-dependent pathways to effect transactivation or transrepression. Recent studies indicate that Sp-family members may functionally interact with ligand-activated nuclear receptors, especially those for steroid hormones. This review provides a discussion of the putative mechanisms and important participants involved in the crosstalk between selected members of this family and the receptor for the pregnancy hormone progesterone, and the relevant outcomes to the control of the transcriptional network in the uterine endometrium.

2. INTRODUCTION

The mammalian uterus is dependent on numerous extracellular signals for its growth and development. At maturity when it undergoes the highly orchestrated cycles of proliferation and differentiation associated with the estrous cycle and pregnancy, and during aging, when these physiological processes begin to slow down and eventually shut off, key signaling molecules act in synergy to regulate the temporal and cell-type specific expression of various gene products that are requisite for the control of these molecular events. A central participant in these regulatory processes is the ovarian steroid progesterone, which albeit normally considered the pregnancy hormone, is nonetheless, closely associated with puberty, the estrous cycle, and reproductive aging. The profound effects of progesterone on cell growth, development, differentiation, and homeostasis are mediated through its specific nuclear receptor, a ligand-activated transcription factor (1). The events initiated by the binding of progesterone to its receptor and leading to the transcriptional activation of numerous target genes have been the subject of excellent reviews (2,3) and will not be described here. However, there are as yet pockets of unknowns in the current understanding of how progesterone mediates its diverse biological effects and even more so, in the identities of genes and their products that constitute progesterone receptor-responsive pathways. More recently, the possible participation of other transcription factors in steroid hormone signaling mechanisms has been reported (4, 5). In this review, we examine the potential contribution of the Sp/KLF family of DNA-binding proteins to the transcriptional control of pregnancy-associated uterine

genes that are correspondingly, targets of ligand-bound progesterone receptor (PR), and demonstrate possible mechanisms of crosstalk in these transcription factors' signaling events.

3. Sp/KLF MEMBERS AND PROGESTERONE RECEPTOR ISOFORMS

The Sp/KLF family members have received much attention over the last 5 years due in part, to the increasing documentation of their existence and involvement in the molecular mechanisms underlying cellular proliferation and differentiation in many tissues and specialized cell types (6-8). There are currently five Sp (Sp1, Sp2, Sp3, Sp4 and Sp5), and fifteen KLF, family members (8). The latter derived its name from its similarity with the *Drosophila* segmentation gene Krüppel, mutations of which cause abnormalities in establishment of body parts (9). Sp and KLF proteins are quite distinct in their primary sequences (10), however, they are classified as belonging to the same transcription factor family based on the presence of three Cys_2/His_2 zinc finger motifs in their carboxy-terminal regions that confer preferential binding affinity for GC/GT-rich sequences within target gene promoters. Members of this family have distinct amino-terminal regions, which contain unique transactivation domains mediating protein-protein interactions requisite for their transcriptional regulatory actions. Sp-family members are characterized by glutamine- and to a limited extent, serine/threonine-rich domains within their N-termini, while there is considerable variability in the corresponding region among KLF members, which may contain acidic, proline-rich, serine-rich, hydrophobic and other types of transactivation domains (7). The functional consequences of these differences are most apparent in the distinct transcriptional activity of family members, which can behave as trans-activators or trans-repressors, depending on cell context and promoter architecture (8). Sp/KLF family members also exhibit substantial differences in their sizes, due mostly to variations in the lengths of their N-termini (11). Sp1 is the largest, consisting of 717 amino acids, while KLF9/BTEB1 is the smallest, with 244 amino acids. Other family members have molecular sizes in between. The ability of KLF members to function as transcriptional activators or repressors does not appear to be related to the lengths of their respective N-terminal regions, but as will be discussed below, is more a function of the specific sequences contained within and which mediate interactions with distinct nuclear protein domains.

The KLF members are designated as xKLF or KLF1-15, where x refers to the tissue in which the gene was first identified (e.g. EKLF, erythroid KLF; GKLF, gut KLF), and 1 to 15, to the chronological order by which the gene was first reported (e.g. EKLF/ KLF1). Others have been given names based on their functional DNA-binding properties (e.g., BTEB for Basic Transcription Element Binding) (12), but all have now been incorporated into a single nomenclature system that describes their phylogenetic relationships (8). Sp family members (Sp1-4) are most related to KLF9/BTEB1 (6), and the recent discovery of Sp5, exhibiting an N-terminal domain that is proline-rich, characteristic of KLF rather than Sp family members, has strengthened this premise and provided the likely evolutionary link between Sp and KLF proteins (11). Sp and KLF members are products of distinct genes with discrete chromosomal locations. In this regard, the genes for human KLF9/BTEB1, UKLF/KLF7, and Sp1 are on chromosomes 9, 2, and 12, respectively (13-15).

In contrast to Sp/KLF transcription factors, the PR in humans and rodents has only two well-characterized isoforms, namely PR-A and PR-B. These proteins are produced from a single gene either by transcription from two distinct promoters or by translation initiation from two alternative AUG sites, and differ only by a stretch of 164 amino acids present in the amino-terminus of PR-B. A novel isoform of human PR (termed isoform S), comprised of exons 4-8 of the PR gene, has been recently described in the testis and to a lesser extent, in the uterine endometrium (16). The physiological relevance of this PR isoform is unclear, although it is possibly related to a previously described cell membrane-associated PR (17). By contrast, the functions of the PR-A and PR-B isoforms have been elucidated using gene knockout approaches (18-20). Results of these studies demonstrated the PR-A and PR-B isoforms to be functionally distinct, with biologic effects specific to a target organ or gene (21). In particular, mice lacking the PR-A isoform are infertile and exhibit severely impaired uterine phenotype characteristic of PR (A and B) null mice, while those with ablated PR-B gene are fertile and exhibit a normal uterine phenotype. The discrete functions have been attributed in part, to the preferential affinity of each isoform for distinct co-factors. For example, human PR-B efficiently interacts with transcriptional co-activators GRIP1 and SRC-1, and less so with the co-repressor SMRT, while the reverse holds true for human PR-A (22). The domain structure of PR has some similarity to that of Sp/KLF members- the carboxy-terminal portion of the protein contains Zn-finger DNA-binding domains, and one of its transactivation domains (AF-1) is localized within the amino-terminal region of the molecule. Unlike the Sp/KLF members, however, PR has a ligand-binding site, and additional transactivation domains (AF-2 and/or AF-3), all of which are necessary for full transcriptional activity. Moreover, dimer (homo- and/or hetero-) formation upon ligand binding is requisite for PR to bind to its DNA response elements. No such requirement has been demonstrated as yet for the basal transactivation or transrepression activity of Sp/KLF proteins, although direct interactions within and among family members, mediated by their respective non-DNA binding domains, can result in super-activation of transcriptional activity (23-25).

Studies on the phenotypes of mice null for the various Sp/KLF family members, albeit currently limited, have provided important insights into these protein's respective physiological functions. Sp1 null embryos are developmentally retarded, and die *in utero* around day 11 of gestation (26). Sp3-deficient embryos, although similarly growth-retarded, survive to term, but immediately die thereafter due to respiratory failure (27). A curious phenotype of these fetuses is a defect in late tooth

formation due to a deficiency in synthesis of dentin and enamel-related proteins. Two laboratories reporting on the phenotypes of Sp4 knock-out mice (28, 29) noted the lack of embryonic lethality, albeit neonatal death occurs within 4 weeks of birth for two-thirds of the offspring, and growth retardation for the surviving litters as well as breeding defects in males accompany the gene ablation. Female mice were also observed to have smaller uteri and to experience delayed sexual maturation (29). The phenotypes generated from KLF members, which exhibit greater tissue- and cell-type specificities as well as diversity in primary structures, are anticipated to be more complex and multi-dimensional. Indeed, inactivation of the erythroid Krüppel-like Factor EKLF/KLF1 resulted in fetal death due to reduced expression of the beta-globin gene (30), while mice lacking LKLF/KLF2, the most related member to KLF1, exhibited embryonic lethality at gestation day 11.5 to 13.5 and multiple defects including craniofacial abnormalities, retarded growth, and anemia (31). Sp/KLF family members are, thus, crucial for tissue growth and development, although they do not necessarily exhibit functional redundancies within a tissue, as would be predicted from the extensive similarities in their DNA-binding properties and expression patterns. Additional studies to ablate other KLF members are presently underway in various laboratories, which should further delineate the distinct as well as overlapping functions of these nuclear proteins *in vivo.*

4. EXPRESSION OF Sp/KLF MEMBERS IN THE UTERINE ENDOMETRIUM

Of the 20 or so presently identified members of the Sp/KLF family, only a few (Sp1, Sp2, Sp3, Sp4, KLF9/BTEB1, and KLF5/IKLF/BTEB2) were shown as being expressed in the mammalian uterine endometrium and associated cell types (32-35; unpublished data from our laboratories). Their distinct localization to the endometrium was largely the consequence of detailed functional analyses carried out on numerous endometrial-associated gene promoter and 5'-regulatory regions which exhibit GC/GT-rich sequences, using a variety of methodological approaches including DNAse I footprinting and methylation protection assays, transient transfection assays of promoter constructs with mutated GC/GT-rich regions, gel retardation "supershifts" with recombinant proteins and their specific antibodies, and measurements of transcriptional activities of promoter constructs upon over-expression of specific Sp/KLF members (36-41). A "uterine phenotype" resulting from genetic ablation of specific family members, as was observed for Sp4 (29), was also considered to be indicative of endogenous uterine expression and function. In human endometrial carcinoma cell lines (i.e., Ishikawa, Hec-1-A, RL95), Sp1, Sp3, Sp4, BTEB1, and BTEB2 are co-expressed, albeit their relative levels appear to differ. The expression of Sp1 and Sp4 (32) as well as of BTEB1 and BTEB2 (unpublished data from our laboratories) has been demonstrated in the mouse uterus; however, their specific patterns of expression have yet to be carefully examined as a function of the estrous cycle or pregnancy. In primary cultures of endometrial cells from pseudo-pregnant rabbits, endogenous Sp1 was shown to mediate the estrogen activation of the uteroglobin gene (42). The expression of KLF9/BTEB1 gene in the pig uterine endometrium was found to be predominantly epithelial cell-associated, coincident with that of the gene for the glandular epithelial-specific transplacental iron transport protein uteroferrin (34). Consistent with this, BTEB1 transactivates the uteroferrin gene promoter in endometrial epithelial, but not in stromal, cells (38). However, unlike uteroferrin, KLF9/BTEB1 protein is ubiquitously expressed across pregnancy (34, 43), suggesting that BTEB1 alone does not confer epithelial-specificity and pregnancy regulation to this gene's expression (38). It is not known whether other Sp/KLF family members exhibit endometrial cell-specific action; however, Sp1 and Sp3 are able to induce the promoter activities of distinct genes in both endometrial stromal and epithelial cells, suggestive of a lack of cell specificity in the transactivation properties of these nuclear proteins (40, 44). The recent demonstration that co-expression of distinct KLF members in the human placenta is correlated with specific stages of development argues for their cooperation in coordinating tissue-specific developmental processes (45).

The uterine endometrial expression of PR isoforms is not strictly temporally or spatially co-incident with those of Sp/KLF family members. Moreover, recent studies have indicated that the expression and localization of distinct PR isoforms to either endometrial stroma or glandular epithelial cell types varies with physiological or pathological status. For example, while PR-A is located in endometrial stromal cells throughout the human menstrual cycle, PR-B is found only in glandular epithelial cells during the mid-secretory phase (46). Morever, only PR-A is detectable in endometriotic tissues (47) and in uterine endometrial cancer cells (48), the latter being a consequence of the preferential inactivation of the PR-B gene by hypermethylation of associated CpG islands. Further, uterine endometrial epithelial expression of PR in many species, although not definitively classified, as either PR-A or PR-B, is cyclical in nature, with levels up-regulated by estrogen and down-regulated by progesterone (49). Interestingly, the stimulatory effects of estrogen on PR-A were reported to be greater than on PR-B (50). Of the Sp/KLF members expressed in the uterine endometrium, no distinct pattern of expression with reproductive status has emerged, a likely consequence of the limited investigations carried out to date on any of these proteins.

5. TRANSCRIPTIONAL ACTIVITY OF Sp/KLF MEMBERS ON PROGESTERONE-REGULATED GENES

A number of uterine endometrial genes whose expression is under the regulation of Sp/KLF transcription factors are similarly modulated by progesterone. Examples of these include rabbit uteroglobin, human IGFBP-1, human tissue factor, porcine uteroferrin, rat insulin-like growth factor-I, and human glycodelin (33, 51-56). Although the expression of these genes are not necessarily pregnancy stage- or uterine-specific, their collective

functions during pregnancy appear to be related to particular aspects of endometrial cell differentiation requisite for conceptus implantation and subsequent growth. Progesterone regulation of these genes' expression has been demonstrated to occur at the transcriptional level, although the induction for each may be transient or delayed, suggesting distinct mechanisms of hormonal control. In addition, the promoter regions for a number of these genes do not contain canonical progesterone-responsive elements (PRE) that typically confer progestin sensitivity to target gene transcription. The finding that GC-rich sites binding Sp/KLF family members are present within most promoter regions that are progesterone-responsive, and the recent demonstration that Sp family members can, by binding to their recognition motifs, mediate transcriptional regulation by steroid hormones have provided a novel regulatory mechanism by which Sp/KLF members can modulate progesterone effects on gene expression. The latter mechanism is best illustrated by the example of the transcriptional control by progesterone of the cyclin-dependent kinase inhibitor $p21^{WAF1}$ gene, which does not exhibit PRE motifs in its promoter region (57). Although this study was carried out in the breast cancer cell line T47D, p21 gene expression is ubiquitous, suggesting that similar mechanisms are likely operative in endometrial cells. The mechanism proposed is that the progesterone/PR complex serves to bridge Sp1 bound to its recognition motif, to transcriptional co-activators and basal transcription factors, leading to the formation of a functional transcriptional complex. In this scenario, physical interactions between the PR dimer and Sp1 occur, which as recent evidence suggests, are likely to be mediated by the carboxyl-terminal DNA-binding domain of Sp1 (58).

The PR is a phosphoprotein that becomes highly phosphorylated upon binding its ligand, and this modification is important for its transcriptional activity. The phosphorylation of distinct sites within PR is controlled by specific kinases, including MAPK (mitogen-activated protein kinase), the cyclin-Cdk2 complex, and casein kinase II (59) and may result in opposing effects on receptor activity (60). At least 14 phosphorylation sites, mostly at the serine-proline motifs, have now been identified in the human PR (61). Some of these are unique to the PR-B form while some are shared with PR-A, and seven of these appear to be substrates for Cdk2 *in vitro* (61). The latter is suggestive of the involvement of the Cdk2 pathway in PR activity. A cell cycle-associated gene whose mRNA level is induced by KLF9/BTEB1 over-expression in the human endometrial carcinoma cell line Hec-1-A, is Cdk2 (41). The possibility that KLF9/BTEB1 regulates cellular Cdk2 levels, the activity of which is important for PR transcriptional function, suggests a potential pathway for cross-talk between PR signaling and that of this KLF family member.

A novel mechanism by which PR and Sp/KLF family members may influence each other's transcriptional activity has been recently demonstrated using human endometrial carcinoma Hec-1-A sublines with high and low expression of KLF9/BTEB1 (43). Sublines with higher BTEB1 expression had increased sensitivity to progesterone in a PR-B-dependent manner, with maximal activity of the transfected reporter construct, which contained recognitions motifs for both PR and BTEB1 in the regulatory sequences, observed at 10-fold lower concentrations of the hormone than in sublines with much diminished BTEB1 expression. The latter was shown to be due to the ability of BTEB1 and ligand-bound PR-B (i.e., PR-B homodimer) to physically interact, forming a functional complex (43). Interestingly, in contrast to the previously documented interaction of PR-B and the Sp/KLF member, Sp1, which was mediated by Sp1 binding sites, rather than by the canonical PRE which are lacking in the $p21^{WAF1}$ gene promoter (57), the functional complex formed between ligand-bound PR-B and BTEB1was also observed in the absence of GC-rich regions that are known to bind BTEB1, and appeared to occur through the PRE. Thus, although the specific mechanisms by which Sp/KLF members promote progesterone-responsive gene expression may differ with promoter architecture, the functional interaction of PR with these family members may be a common phenomenon in progesterone target cells.

6. CO-ACTIVATORS AND CO-REPRESSORS OF PROGESTERONE RECEPTOR AND Sp/KLF TRANSACTIVATION FUNCTIONS

A number of co-activators and co-repressors that are required for transcriptional control by nuclear receptors, including that for progesterone, have now been identified (62, 63). These nuclear receptor-interacting proteins were isolated by various approaches including yeast two-hybrid, far-Western, and expression cloning, using the transactivation domains of a broad range of nuclear receptors as "bait" (63). Co-activators appear to modulate transcription by interacting with nuclear factors bound to their cognate elements within gene promoters; this results in the formation of a stable multi-subunit coactivation complex with components of the general trancription machinery for the initiation of RNA Polymerase action. A large number of nuclear activators fall under the category of Histone Acetylases (HATs), which are now widely regarded to be crucial for transcriptional activation, not only for their role as chromatin modifiers through their ability to acetylate lysine residues within histones, but also as specific modifiers of transcription factors (64, 65). The findings that PR (66) and several Sp/KLF members interact with and are distinct subtrates of several well-known HATs, which include CREB binding protein (CBP) and its homolog p300, p300/CBP associated factor (P/CAF) and Steroid Receptor Coactivator-1 (SRC-1) (67-69), suggest commonality in the mechanisms underlying these factors' transcriptional activities, and more intriguingly, the likelihood of these proteins to be engaged as co-members of a functional coactivation complex. Similar to PR, Sp1, FKLF2/KLF13/BTEB3, KLF1/EKLF and GKLF/KLF4 physically interact with p300/CBP (70-72), and acetylation of FKLF2/KLF131/BTEB3 and KLF1/EKLF enhanced their respective transcriptional activities towards target promoters. Further, upon acetylation, EKLF exhibited a higher affinity for the SW1/SNF chromatin remodeling family (73), and this interaction, specifically with two

SW1/SNF subunits, namely BRG1 and BAF1, is requisite for its transcriptional activity (73, 74). Interestingly, however, distinct HATs may fulfill the acetylation requirements for these transcription factors; indeed, while KLF1/EKLF is superactivated by CBP/p300, but not P/CAF (70), FKLF2 is a substrate for all three HATs (72). Our recent observations (Zhang X-L, Zhang D, Simmen, FA and Simmen RCM, manuscript in preparation) from transient transfection studies using human endometrial epithelial cells, that the transcriptional activity of KLF9/BTEB1 is enhanced by the addition of human CBP expression vector, but only in the presence of liganded PR-B, points to the selective utilization of co-activators by KLF family members to achieve functional specificity. Thus, functional redundancy of co-activators may not apply to KLF members, as has been suggested for nuclear receptors (62, 63). A mechanism employed by PR, when bound to antagonists rather than agonists, resulting in transcriptional repression (75) also appears to be utilized by certain KLF members acting as repressor proteins. BTEB3 and BKLF2/KLF8 were recently shown to recruit and interact with the co-repressor proteins histone deacetylase-1 (HDAC) and mSin3A, the latter occurring through the conserved alpha-helical repression motif that is common to other transcriptional repressors (76-78). Consistent with its function as a trans-activator or trans-repressor of gene promoter activity, BTEB3 can bind both HAT and mSin3A.

A novel nuclear receptor co-regulator, termed SNURF (for small nuclear RING finger protein) that was initially isolated using the DNA-binding domain of the androgen receptor as "bait" in yeast two-hybrid assay, has also been shown to mediate PR-dependent transactivation (79). The possibility that SNURF may also serve as a link between PR- and Sp/KLF-mediated target gene transactivation is suggested by the observations that Sp1 physically interacts with SNURF via the latter's C-terminal RING finger domain, which is distinct from the N-terminal region recognized by steroid hormone receptors (80). Other KLF member-interacting proteins have also been identified that are not utilized for ligand-dependent PR transactivation; these include the co-repressor protein CtBP (carboxyl-terminal Binding Protein) which binds KLF8 and BKLF/KLF3 (76, 81), and the Zn-finger domain of GATA-1, which binds Sp1 and EKLF (82). Thus, although PR and KLF members may employ a general mechanism for superactivation involving common co-interacting proteins, this does not necessarily preclude the use of distinct pathways that may confer specificity to Sp/KLF members within the context of cell and promoter functions.

7. REGULATION OF Sp/KLF GENE EXPRESSION

Sp/KLF members, while belonging to the same family of DNA-binding proteins, are distinctly regulated. By virtue of their perceived roles as largely "housekeeping" transcription factors, the expression of genes encoding Sp1 and its closely related members (e.g., Sp2, Sp3, Sp4) are considered to be constitutive, and their activities are altered mostly through protein modifications involving phosphorylation events. Indeed, Sp1 and other members of this family are targets of the cyclin A/CDK complex (83), and their phosphorylation status has been correlated with distinct biological processes including differentiation and apoptosis (84). The recent findings that P regulation of the Tissue Factor gene in human endometrial stromal cells occurs through the induction of Sp1 and the concomitant inhibition of Sp3, gene expression, resulting in altered nuclear Sp1/Sp3 ratios, is the first demonstration of the hormonal regulation of these transcription factors (40). Consistent with this, pregnancy status in mice was correlated with changes in the nuclear profiles of Sp1 and Sp3 proteins, which were distinct for uterine endometrium and mammary gland (85). Members of the KLF family, however, appear to be more subject to hormonal control, consistent with their presumed distinct tissue, cell- and developmental-associated expression, although these studies remain quite limited and largely absent for endometrial cells. KLF5/BTEB2 mRNA levels were induced by the phorbol ester PMA and basic fibroblast growth factor in vascular smooth muscle cells, and this was shown to occur at the level of its promoter (86). KLF5 was also identified in the mouse mammary epithelial cell line C57MG, as a downstream target gene for Wnt-1 signaling through a protein kinase C transduction pathway (87). KLF9/BTEB1 gene expression was induced by thyroid hormone in Neuro-2A cells, consistent with the observed increase in the levels of BTEB1 transcripts in developing rat brain (88). In hepatic stellate cells, acetaldehyde increased BTEB1 mRNA levels, a process transduced by the stress-related JNK system (89). In porcine endometrium, BTEB1 mRNA and protein levels did not change across pregnancy (34, 43), suggesting that at least in this tissue and in this species, BTEB1 is refractory to steroid hormone control. In breast tumors and immortalized human mammary epithelial cells, KLF4/GKLF gene expression, measured at the levels of both mRNA and protein, is increased relative to normal tissues and non-transformed mammary epithelial cell lines (90). Since normal mammary epithelial cells are major targets of the steroid hormones estrogen and progesterone, the latter mostly mediated by the PR-B isoform (18, 19), and the receptor levels for estrogen and progesterone are altered in normal vs. neoplastic tissues (91), this finding suggests potential control by estrogen and/or progesterone, of the expression of this KLF member.

A hint of regulation by Sp/KLF members of PR gene expression is provided by a recent study demonstrating the presence within the promoter region of the human PR-A, of two Sp1-binding sites, that together with an estrogen response element half-site, mediates estrogen responsiveness of this promoter in transient transfection studies (92). Little is known about a similar regulation of the PR-B isoform gene expression by any of the Sp/KLF members.

8. PERSPECTIVES

The emerging crosstalk between specific members of the Sp/KLF family and ligand-bound PR, albeit quite limited in scope at the present time, imply that the multiple transcriptional regulatory pathways mediated by PR in normal endometrial cells are complex and far

from being well understood. In this regard, considerations for the further elucidation of these pathways should include: a) a detailed description of the temporal and spatial patterns of expression of distinct Sp/KLF family members in uterine endometrium, including their regulation by steroid hormones and by autocrine/paracrine-acting endometrial growth factors; b) the identification and analysis of additional progesterone-responsive genes for the involvement of uterine-expressed Sp/KLF members, including whether these interactions occur by direct and indirect mechanisms; c) *in vivo* manipulation of the expression of these family members, alone and in combination, either by "knock-in" or "knock-out" of corresponding genes, and analysis of the functional consequences on endometrial tissue growth and differentiation, including loss or gain of progesterone-sensitivity; d) investigation of the potential competition between PR and Sp/KLF members for the limiting amounts of co-factors within the context of target promoters and physiological status; and e) the dissection of the functional domains involved in the "crosstalk" between PR and Sp/KLF members by mutational analysis. Given that the involvement of Sp/KLF members on target gene transactivation is also common to the signaling mechanisms mediated by other steroid hormone receptors (93, 94), parallel analyses of their interactions with these nuclear receptors, and consequences thereof on hormone-mediated cellular events, will likely facilitate further understanding of the critical aspects of steroid-dependent functions in reproduction and normal tissue growth that significantly impact human health.

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Abbreviations: KLF: Krüppel-like Factor; BTEB: Basic Transcription Element Binding; PR: progesterone receptor; IGFBP1: insulin-like growth factor-binding protein-1; PRE: progesterone-responsive element; MAPK: mitogen-activated protein kinase; Cdk: cyclin-dependent kinase; Hec-1-A: human endometrial carcinoma-1-A; CBP: CREB binding protein; p/CAF: p300/CBP associated factor (PCAF); SRC-1: steroid receptor coactivator-1; HAT: histone acetylase; HDAC: histone deacetylase; SNURF: small nuclear ring finger protein; CtBP: carboxyl-terminal binding protein.

Key Words: Sp/KLF, Progesterone Receptor, Uterine Endometrium, Transcriptional Control, Review

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