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Review Article

Prohibitins in Reproduction- A Timeline

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Abstract

Prohibitins are ubiquitous and an evolutionary conserved protein family that is present in multiple cellular organelles including mitochondria in addition to the nucleus. The Prohibitins are involved in multiple cellular functions such as cellular differentiation, anti-proliferation, morphogenesis and play a major role in maintaining the functional integrity of the mitochondria. Our laboratory and other groups have performed experimental studies on the expression and distribution pattern of prohibitins in various reproductive tissues of different species, which are include mice, rats, pigs, humans and few lower vertebrates and invertebrates. Moreover, recent studies have shown that prohibitins are strongly associated with spermatogenesis, folliculogenesis and the functions of the accessory reproductive organs. In this brief review, we highlight experimental evidence that supports the conserved roles that the prohibitins play in reproductive physiology.

Keywords: Prohibitin (PHB); Repressor of estrogen activity (REA); Reproduction

Introduction

Sexual reproduction is a complex multistep hormonal dependent process where a male gamete, the spermatozoa, fertilizes a female gamete, the ova to form a zygote. In vertebrates, the formation of a mature ova and a sperm are through the process of ovarian folliculogenesis and spermetogenesis respectively under the control of endocrine factors including gonadotropins (follicle stimulating hormone, FSH and luteinizing hormone, LH). During these processes, multiple autocrine and paracrine factors, and steroid hormones play important roles as regulators of folliculogenesis and spermatogensis. The coordinated biosynthesis of steroids in the ovary and the testis are critical for progression of the reproductive cycle, successful ovulation and release of spermatozoa, and eventually fertilization and pregnancy. The binding of gonadotropins to specific membrane G-protein coupled receptors (GPCRs), leads to the activation of multiple signal transduction pathways, including the adenylate cyclase-/cAMP-dependent protein kinase A (PKA) pathway, mitogen-activated protein kinase (MAP kinase) signaling and calcium-/calmodul independent pathways that are known to be involved in the regulation of steroidogenesis and gametogenesis in vertebrates. Furthermore, multiple cross-talk among these signal transduction systems has been well documented. Interestingly, several other proteins are involved in the process of gametogenesis and interacting regulatory pathways.

Prohibitins are ubiquitous and evolutionary conserved protein family that belongs to the SPFH family which is characterized by the presence of the stomatin/prohibitin/flotillin/HflK/C (SPFH) domain (also known as the PHB domain). Members of this protein family include prohibitin (PHB/PHB1), repressor of estrogen activity (REA/PHB2), stomatins, plasma membrane proteins of *Escherichia coli* (HflKC), flotillins, the human insulin receptor (HIR) proteins, the stomatin-like-proteins (SLPs), podocin and the erlins and plant defense proteins [1,2]. Based on extensive database analysis approximately 1800 PHB domain-containing proteins exist which includes 340 animal proteins and 142 mammalian proteins that are present across all organisms. Currently our understanding of the complex biology of the prohibitins in reproductive physiology is limited. However, our laboratory and other groups have performed a number of experimental studies on the expression and distribution pattern of PHB and REA in various reproductive tissues of different species. These studies are performed in mice, rats, pigs, humans and few lower vertebrates and invertebrates including the red crayfish *Cherax quadricarinatus*, *Octopus tankahkeei*, Chinese mitten crab *Eriocheir sinensis*, *Danio rerio*, *Gallus gallus*, *Salmo salar*, and *Bos taurus*. Moreover, recent studies have shown that prohibitins are strongly associated with spermatogenesis, folliculogenesis and functions of the accessory reproductive organ. In this brief review, we highlight some of the experimental evidence supporting a conserved role for the prohibitins in reproductive physiology.

Prohibitins

In humans, the PHB gene (hPHB) spans ~11 kb with 7 exons and map to chromosome locus 17q21 [3]. The first exon and a small portion of the second exon comprise the 5' untranslated region, whereas the largest exon, exon 7 contains ~700 bp of 3' untranslated RNA. Several transcripts of the PHB gene are transcribed with varying lengths of 3' untranslated region [4]. The longer transcripts are present at higher levels in proliferating tissues and cells [5]. The abundance of PHB mRNA is inversely related to markers of cellular proliferation in different cells and tissues [6-10]. Comparative genomic alignment studies have shown that the human and rat PHB genes are similar except for intron 2 and 3, which are ~1 kb larger in the rat gene [11]. The hPHB gene encodes ~30 kDa protein, also known as B-cell receptor associated protein-32 (BAP32) gene. PHB contains four highly conserved domains, namely, an N-terminal hydrophobic domain; a PHB domain (amino acid residues 26-187) encoded by exon 3, 4 and 5, and which is conserved from protozoa to mammals; a coiled-coil (CC) alpha helices domain (amino acids residues 177–211) present at the C-terminal end of the protein, and encoded largely by exon 6; and a putative nuclear export sequence (amino acid residues 257 to 270) which present at the C-terminal.

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Table 1: Prohibitins role in female reproduction.

Year and References	Critical findings
[27]	• Identified and characterized prohibitin (PHB) as an intracellular protein (p28 kDa) during differentiation of rat granulosa cells (GCs) isolated from preantral and early antral follicles.
[28]	• PHB was localized within rat GCs of infant and juvenile ovaries. • A strong expression pattern of PHB in rat oocyte at all stages of follicular development, in rat corpus luteum and in follicles undergoing atresia.
[29]	• PHB roles were confirmed in mitochondrial structure and function during growth and differentiation of GCs.
[30]	• PHB gene expression profiles were analyzed in normal and in carcinoma-induced female rat mammary gland.
[25]	• Demonstrated the roles of prohibitin (PHB and REA) complex for *Caenorhabditiselegans* (*C. elegans*) embryonic development, and necessary for normal mitochondrial morphology and respiration.
[31]	• GnRH dependent PHB expression is important for maturation of T lymphocytes and rat thymic growth.
[32]	• PHB was immunolocalized in rat GCs, theca-interstitial cells, and the oocyte; and in porcine oocytes, zygotes, and blastocyst. • Gonadotropin dependent PHB expression was inversely correlated to PCNA expression during follicular maturation and positively co-localized with P450scc. • In atretic follicles, germinal vesicle-stage oocytes, zygotes, and blastocysts PHB was translocated from the cytoplasm to the nucleus.
[33]	• In human fundus, the expressions of repressor of estrogen receptor activity (REA) is reduced during labor, and suggest that REA gene is involved in regulatory pathways of estrogen receptor alpha (ERA) activity.
[34]	• REA is required for the maintenance of estrogen receptor (ER) activity and normal mammary gland development. The reduction or loss of REA function promotes over-activation of ER and increase breast cancer risk in humans.
[35-37]	• In rat GCs, mitochondrial PHB act through phospho-PHB (pPHB)-MEK-pERK pathway and regulates the Bcl/Bcl-xL which inhibit Bax-Bak expression. These events directly inhibit the release of cytochrome c from the inter-mitochondrial space and inhibit downstream activation of cleaved caspase 3.
[38]	• In rainbow trout (*Oncorhynchusmykiss*), a higher REA mRNA abundance in eggs inhibits development of embryo.
[39]	• Demonstrated a novel mechanism for control of estrogen-induced luminal epithelial proliferation involving uterine endometrial stromal (ST) Krüppel-like factor 9 (KLF9) regulations of paracrine factor(s) to repress epithelial expression of co-repressor REA/PHB2 in mice.
[40]	• PHB was found to be an estrogen-regulated gene essential for uterine development and function in mice, and selectively required for estrogen-regulated gene expression in uterus.
[41]	• Studies demonstrated that REA is essential for mammary gland development and has a gene dosage-dependent role in the regulation of stage-specific physiological functions of the mammary gland during pregnancy and lactation stages.
[42]	• In cloned placenta of domestic cat (*Feliscatus*), the expression of PHB and cathepsin D (CD) were correlated with the generation of reactive oxygen species (ROS), leading to decreased mitochondrial membrane potential and telomeric DNA, which are associated with cellular senescence and apoptosis. The abnormal PHB protein patterns were associated with impaired development, and hence decreased fetal viability.
[43]	• REA expression was intense in both the perinuclear cytoplasm and the nucleus in GCs from follicles at all stages of development in bovine. However, REA expression was less intense in thecal tissue.
[44,45]	• PHB was regulated by follicle stimulating hormone (FSH) in a follicular stage-dependent manner *in vitro* in pre-antral GCs isolated from diethylstilbestrol (DES) treated rats and antral GCs isolated from equine chorionic gonadotropin (eCG)-treated rats.
[46]	• REA physiologically restrained human endometrial stromal cell decidualization, controlling the timing and magnitude of decidualization to enable proper coordination of uterine differentiation with concurrent embryo development that is essential for implantation and optimal fertility.
[47]	• The aberrant expression of glycolysis-related enzymes in human endometrioma tissue was associated with enhanced glycolytic metabolism. The malignant-like feature may be partially caused by low-expression of PHB gene in endometriotic stromal cells.
[48]	• In humans, REA modulated crosstalk among multiple cell types in the uterine tissue and host background, serving as a brake on the estradiol-ER axis and restraining multiple aspects that contribute to the pathologic progression of endometriosis.
[49]	• Folicle stimulating hormone (FSH)-dependent PHB/pPHB upregulation in GCs is required to sustain the differentiated state of GCs.

The N-terminal hydrophobic domain is critical for its attachment to the mitochondrial inner membrane, whereas the CC-domain is important for protein–protein interactions.

The human PHB2 (REA/hPHB2) [12], also referred as prohibitone [13]/B-cell receptor associated protein-37 (BAP37) [14] gene (PHB2) is located at chromosome 12p13 [15]. This gene has 10 exons, with smaller introns than PHB and spans ~5.3 kb. The REA/PHB2/BAP37 gene encodes a protein of ~37 kDa. Similar to PHB structure, REA has a PHB domain, which is encoded by residues 39–201; a CC-domain present at the C terminal end of the protein; a putative signal peptide (residues 1–36), and a putative nuclear localization signal peptide (residues 86–89). In eukaryotes PHB and PHB2 have highly conserved PHB domains. The PHB protein is 54% homologous with PHB2 [16,17] and has a single amino acid difference between rodents and humans [11]. Orthologues of the PHB gene have been identified in several organisms including bacteria [18,19], plants [20,21], *Trypanosoma brucei* [22], *Saccharomyces cerevisiae* (yeast) [23,24], *Caenorhabditis elegans* [25] and *Drosophila* [26].

Prohibitins and Reproduction

Distinct differences in PHB and PHB2 (REA) levels have been observed during ovarian folliculogenesis, spermatogenesis, in mammary gland development, and in uterine tissue. Immunolocalization, Western blotting and immunogold staining of ovaries and testis had shown that both PHB and PHB2 (REA) are present in multiple cellular locations including mitochondria and nucleus, suggesting that they play additional roles in those cellular compartments. Due to complex post-translational modification and changes in cellular localization occurring during different physiological states, it has been difficult to identify the distinct roles that these prohibitins isoforms play in reproductive organs. Currently ours and other research groups are trying to understand the functional roles that the prohibitins play in reproduction by

Table 2: Prohibitins role in male reproduction.

Year and References	Critical findings
[5]	• Identified and characterized prohibitin (PHB) as an intracellular protein (p30 kDa) in rat seminiferous epithelium. • PHB protein was constitutively present in adult Leydig cells and Sertoli cells at all stages.PHB protein were very low in preleptotene spermatocytes, very high in leptotene spermatocytes, and very low in zygotene spermatocytes. • In pachytene spermatocytes, PHB was very high in stages VII-XI and was minimal during stages XII and XIV. • No PHB protein was detected in spermatogonia and spermatocytes.
[50]	• PHB was identified as one of the ubiquitinated substrates that makes the sperm mitochondria recognizable by the egg's ubiquitin-proteasome dependent proteolytic machinery after fertilization and most likely facilitates the marking of defective spermatozoa in the epididymis for degradation.
[51]	• PHB protein was identified and characterized in cephalopod *Octopus tankahkeei* (*O. tankahkeei*) during spermiogenesis.
[52]	• PHB cDNA was cloned and sequenced from testes of the crab *Eriocheirsinensis*.
[53]	• The PHB gene and its protein were characterized in crayfish (*Cherazquadricarinatus*) during spermatogenesis and PHB protein was localized in the innermitochondrial membranes of sperm • The strongest PHB signal was found in spermatogonia, and lower levels in secondary spermatocytes, and weak or absent expression in mature sperm.
[54]	• Demonstrated a role for PHB in GnRH-induced cell death in mature gonadotropes, which is crucial for the normal development and function of the reproductive axis.
[55]	• PHB was co-localized in mitochondria from the late stage of spermiogenesis of macrura crustacean species, *P. clarkia*.
[56]	• PHB gene was cloned and characterized in the Chinese fire-bellied newt *Cynopsorientalis*, and expressed during spermatogenesis and spermiogenesis. • PHB existed during the whole period of spermatogenesis and spermiogenesis. In the mature germ cells, the signals of prohibitins were weak and aggregated at the end of the cell, where as in the sertoli cells had abundant PHB concentrations.

utilizing conditional knock-out mice. We have highlighted a few important findings on the functional roles that PHB and REA play in reproductive physiology in Table 1 and 2.

Conclusion

At present, we are just beginning to understand the critical roles that PHB and PHB2 (REA) play in ovarian, uterine, mammary gland, testis and accessory reproductive organ functions. Although current knowledge indicates that PHB and REA are involved in regulating the fate of folliculogenesis, spermatogenesis and other reproductive processes. A number of basic questions still remain to be answered. These include physiological role that PHB and PHB2 (REA) play in regulating gene expression and signaling in spermatogenesis, folliculogenesis, and the functions of the accessory reproductive organs.

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