REPRODUCTION
REVIEW

Multiple roles of the prostaglandin D_2 signaling pathway in reproduction

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Abstract

Prostaglandins signaling molecules are involved in numerous physiological processes. They are produced by several enzyme-limited reactions upon fatty acids, which are catalyzed by two cyclooxygenases and prostaglandin synthases. In particular, the prostaglandins E_2 (PGE_2), D_2 (PGD_2), and F_2 ($PGF_{2\alpha}$) have been shown to be involved in female reproductive mechanisms. Furthermore, widespread expression of lipocalin- and hematopoietic-PGD_2 synthases in the male reproductive tract supports the purported roles of PGD_2 in the development of both embryonic and adult testes, sperm maturation, and spermatogenesis. In this review, we summarize the putative roles of PGD_2 signaling and the roles of both PGD_2 synthases in testicular formation and function. We review the data reporting the involvement of PGD_2 signaling in the differentiation of Sertoli and germ cells of the embryonic testis. Furthermore, we discuss the roles of lipocalin-PGD_2 synthase in steroidogenesis and spermatogenesis, in terms of lipid molecule transport and PGD_2 production. Finally, we discuss the hypothesis that PGD_2 signaling may be affected in certain reproductive diseases, such as infertility, cryptorchidism, and testicular cancer.

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Introduction

Prostaglandins (PGs) derived from polyunsaturated fatty acids belong to the superfamily of eicosanoids. The eicosanoid cascade starts with the activation of phospholipases A2 and C that release arachidonic acid from the cellular membrane. Arachidonic acid is oxidized and then reduced by the enzymes cyclooxygenases 1 and 2 (COX1 and COX2, also referred to as prostaglandin endoperoxidase H synthase 1 and 2 (PTGS1 and PTGS2)), to be converted into PGG_2 and PGH_2. The COXs are key enzymes in PG biosynthesis and differ in their expression levels and tissue distribution; COX1 is constitutively expressed, whereas expression of COX2 is induced (Simmons *et al*. 2004). PGH_2, the unstable reaction intermediate, is then converted into either PGD_2, PGE_2, $PGF_{2\alpha}$ or prostacyclin (PGI_2) and thromboxane A_2 (TxA_2), by the action of specific terminal PG synthases: prostaglandin D synthase (PGDS), prostaglandin E synthase (PGES), prostaglandin F synthase (PGFS) or prostacyclin synthase (PGIS), or thromboxane synthase (TXS) respectively (Fig. 1 and Table 1) (Cha *et al*. 2006). PGs are rapidly inactivated by oxidation by the NAD+-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH) (Fincham & Camp 1983). PGs are involved in the cardiovascular, gastrointestinal, genitourinary, endocrine, respiratory, immune, and nervous systems (Hata & Breyer 2004). These molecules act locally in an autocrine and/or paracrine manner and their actions are complex, not least because, given the structural similarity of these molecules and their receptors, PGs may have synergistic or antagonistic effects upon the same physiological processes (Woodward *et al*. 2011, Tootle 2013).

PGD_2 is actively produced in many organs, and is the most abundant prostanoid in the CNS (Urade & Hayaishi 2000*a*) and in the respiratory tract and airways of asthmatic patients (Oguma *et al*. 2008). PGD_2 has essential roles in various physiological processes (Matsuoka *et al*. 2000, Kobayashi & Narumiya 2002, Qu *et al*. 2006, Huang *et al*. 2007, Taniguchi *et al*. 2007, Oguma *et al*. 2008, Gao *et al*. 2009, Nieves & Garza 2014), and particularly in several steps of the reproduction function (this function will be discussed further in the following paragraphs). Also, PGD_2 together with the prostaglandins PGE_2 and PGI_2, in conjunction with other mediators such as histamine, are involved in the inflammation process (Hata & Breyer 2004, Herlong & Scott 2006). Hematopoietic PGDS (H-PGDS) is the key enzyme in the synthesis of PGD_2 in the immune system and mast cells (Urade & Hayaishi 2000*a*, Kanaoka & Urade 2003). Furthermore, the resolution of inflammation is accompanied by a shift from the biosynthesis

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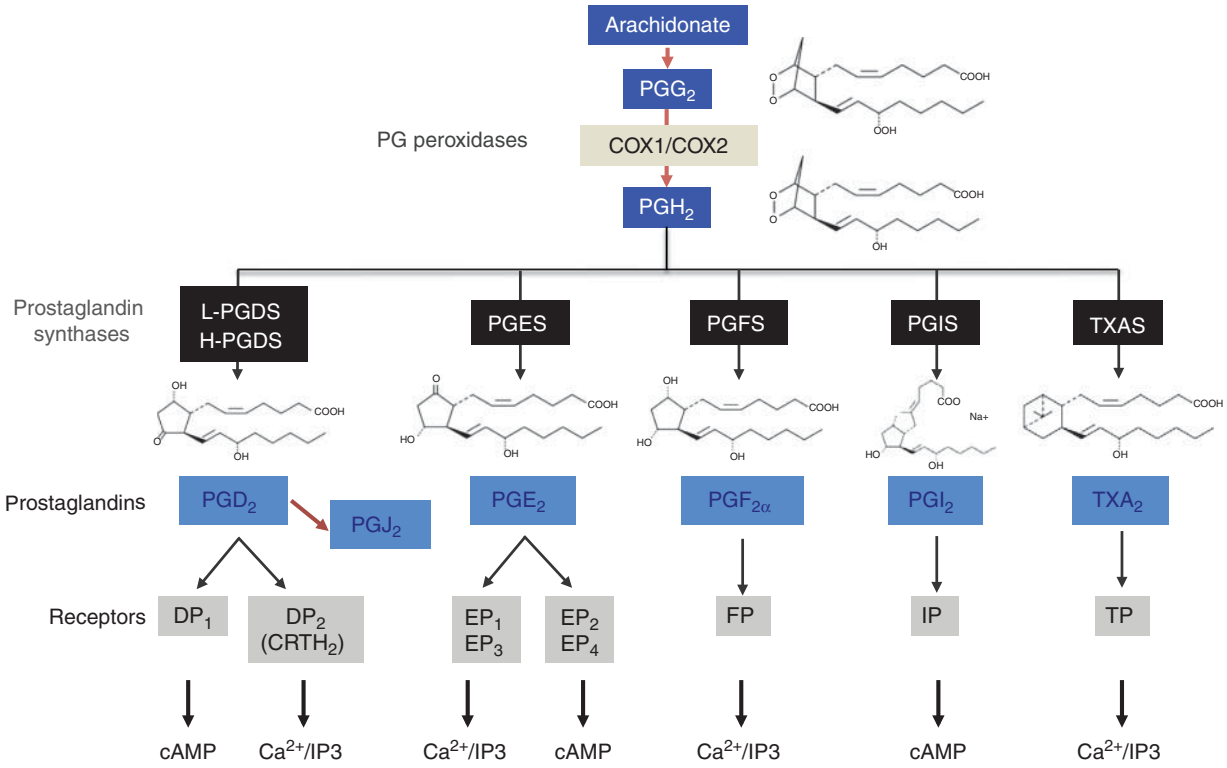

Figure 1 Pathway of prostanoid biosynthesis and signaling. Arachidonic acid is metabolized by the action of cyclooxygenase (COX) first to prostaglandin endoperoxide (PGG_2) and then to PGH_2, which is subsequently converted to various prostaglandins (PGD_2 and PGJ_2, PGE_2, $PGF_{2\alpha}$, PGI_2) and thromboxane A_2 (TXA_2) by respective synthases. COX, cyclooxygenase; PGES, prostaglandin E synthase; PGDS, prostaglandin D synthase; PGFS, prostaglandin F synthase; PGIS, prostacyclin synthase; TXS, thromboxane synthase. Individual prostaglandin interacts with specific members of the subfamily of the G protein-coupled receptor (GCPR) superfamily of seven transmembrane-spanning proteins, DP_1, DP_2, EP_{1-4}, FP, IP, and TP. Then, these receptors activate different transduction (cAMP/ Ca^{2+}) and signaling pathways.

of PGES to that of lipocalin PGDS (L-PGDS) (Schuligoi *et al.* 2005, Nicolaou *et al.* 2014).

PGD_2 synthesis and its regulation

PGD_2 synthesis is regulated by the functional and differential coupling of COX1 and COX2 enzymes with both PGDS and PGES (Ueno *et al.* 2005). The expression of COX2 is induced by growth factors such as pro-inflammatory cytokines (IL1, TNFα), and inhibited by glucocorticoids and other anti-inflammatory cytokines (IL4 and IL10) (Loftin *et al.* 2002, Morita 2002). In particular, COX2 is induced by interleukin-1 in the testes of infertile men, stimulating the production of PGD_2 and $PGF_{2\alpha}$ (Matzkin *et al.* 2010). Testosterone induces COX2 expression and $PGF_{2\alpha}$ production in hamster Leydig cells through a nonclassical mechanism involving MAPK signaling (Matzkin *et al.* 2009). Silencing of *Ptgs2* through G9a- and EZH2-mediated histone methylation and DNA methylation of its promoter region has also been reported (Coward *et al.* 2014). On the other hand, the nonsteroidal anti-inflammatory drugs (NSAIDS) inhibit COX enzymatic activities through noncompetitive (Aspirin) or competitive binding to the active site (Cha *et al.* 2006).

The synthesis of PGD_2 is under the specific control of two PGDS, the L-PGDS (or PTGDS), and the H-PGDS (or PTGDS2) (Urade & Eguchi 2002). Originally identified in the rat brain, L-PGDS, whose function is independent of the tripeptide glutathione, is part of the lipocalin protein superfamily, the members of which are secreted into the extracellular space (Urade *et al.* 1985, Urade & Hayaishi 2000*a*). This enzyme is produced in the CNS (brain, spinal cord, dorsal root ganglia), in the male genitalia (testes, epididymides, prostate) (Fouchecourt *et al.* 2002), and in the heart (Eguchi *et al.* 1997). It has been suggested that L-PGDS has dual functions. Associated with the endoplasmic reticulum and the outer nuclear membrane, it catalyzes the final step in PGD_2 synthesis from a common PG precursor. Secondly, as L-PGDS is secreted in many fluids (cerebrospinal fluid, seminal plasma, ascites, serum, urine, and amniotic fluid), it has been proposed to have a role in binding and transporting small hydrophobic ligands such as retinol, β-lactoglobulin, bile pigments, and thyroid hormones (Urade & Hayaishi 2000*b*, Fouchecourt *et al.* 2002).

The expression of *L-Pgds* is also under the control of many regulatory factors, protein kinase C (PKC) (Fujimori *et al.* 2005), estrogens (Mong *et al.* 2003), IL1β, RasGRP4

Table 1 Abbreviations.

COX1 or PTGS1: Cyclooxygenase 1 or prostaglandin G/H synthase 1
COX2 or PTGS2: Cyclooxygenase 2
DP_1: Prostaglandin D_2 receptor 1
DP_2 or $CRTH_2$: Prostaglandin D_2 receptor 2
H-PGDS or PTGDS2: Hematopoietic-type prostaglandin D_2 synthase
HQL-79: 4-benzhydryloxy-1-[3-(1H-tetrazol-5-yl)-propyl]-piperidine
L-PGDS or PTGDS: Lipocalin-type prostaglandin D_2 synthase
NSAIDS:
PG: Prostaglandins
PGD_2: Prostaglandin D_2
PGDS: Prostaglandin D synthase
PGE_2: Prostaglandin E_2
PGES: Prostaglandin E synthase
$PGF_{2\alpha}$: Prostaglandin $F_{2\alpha}$
PGFS: Prostaglandin F synthase
PGG_2: Prostaglandin G_2
PGH_2: Prostaglandin H_2
PGI_2: Prostaglandin I_2 or prostacyclin
PGIS: Prostaglandin I synthase
TxA_2: thromboxane A_2
TXS: Thromboxane A synthase

(Li *et al*. 2003), each being highly cell-type specific. PGD_2 itself induces *L-Pgds* expression through binding of the Nrf2 factor on the *L-Pgds* promoter region in macrophages (Kim *et al*. 2013). *In vitro* primary cultures of rat Sertoli cells also show the activation of L-PGDS protein expression after treatment with progesterone or retinoic acid (RA) (Samy *et al*. 2000). RA strongly induces the accumulation of *L-PGDS* mRNA in human 3AO ovarian cancer cells, leading to the inhibition of their proliferation (Su *et al*. 2003). Furthermore, in the embryonic male gonad, *L-PGDS* expression is initiated and maintained by the testis differentiating factor SOX9 (Moniot *et al*. 2009) (see below).

Originally identified in the rat spleen, H-PGDS is a member of the class of glutathione-S-transferase enzymes, which are cytosolic and play a role in detoxification. Bivalent Ca^{2+} and Mg^{2+} ions increase the activity of H-PGDS; however, only Mg^{2+} increases its affinity for glutathione (Inoue *et al*. 2003). Despite the high homology of the primary sequence in different species, the tissue expression profile is highly variable. Expression is high in the peripheral tissue, spleen, thymus, bone marrow, gastrointestinal tract, and oviduct of rats (Kanaoka & Urade 2003). In the mouse, expression is predominant in the skin, oviduct (Kanaoka *et al*. 2000), and granulosa cells of the postnatal and adult ovary (Farhat *et al*. 2011). However, in humans, expression is found in the placenta, lung, fetal liver, heart, brain, mastocytes, lymphocytes, Th2 cells, and antigen-presenting cells (Kanaoka *et al*. 2000, Tanaka *et al*. 2000).

PGD_2 is dehydrated *in vitro* and *in vivo* by a nonenzymatic process to produce PGs of the J series, PGJ_2, and 15-deoxy $^{12-14}$-PGJ_2 (15-d PGJ_2) (Shibata *et al*. 2002). These PGD_2 metabolites can also influence diverse cellular functions. In particular, H-PGDS was shown to control the onset and resolution of acute inflammation through PGD_2 and 15-d PGJ_2 (Rajakariar *et al*. 2007).

PGD_2 signal transduction

PGs are secreted and activate nine different receptors (Fig. 1): DP_1 and DP_2 or chemoattractant receptor-homologous molecule expressed on Th2 cells ($CRTH_2$) for PGD_2, EP_{1-4} for PGE_2, FP for $PGF_{2\alpha}$, IP for PGI_2, and TP for TxA_2 (Breyer *et al*. 2001). PG receptors are categorized as three clusters of a distinct subfamily of the G protein-coupled receptor (GCPR) superfamily of seven transmembrane-spanning proteins (Coleman *et al*. 1994). The only exception is DP_2, a member of the chemoattractant receptor subgroup. These receptors transduce different signals via the production of second messenger cAMP or IP3/diacylglycerol/Ca^{2+} (Woodward *et al*. 2011) (Fig. 1).

Thus, PGD_2 may bind to two receptors, the DP_1 receptor (Boie *et al*. 1995) and/or the DP_2 receptor $CRTH_2$ (Hirai *et al*. 2001). Activation of the DP_1 receptor, coupled to a Gαs protein, induces the production of the second messenger cAMP, which stimulates protein kinase A (PKA) and also induces an influx of Ca^{2+} (Boie *et al*. 1995). The activation of $CRTH_2$ or DP_2 receptors coupled to a Gαi protein inhibits cAMP production (Hirai *et al*. 2001) and induces intracellular Ca^{2+} mobilization caused by the production of inositol triphosphate (Woodward *et al*. 2011). On the other hand, the PGD_2 metabolite 15d-PGJ_2 was identified as a ligand for the peroxisome proliferator-activated receptor gamma (PPARγ), a member of the nuclear receptor family (Forman *et al*. 1995) and for DP_2.

PGD_2 and reproduction in adult gonads

Female reproduction

Few studies have evaluated the involvement of PGD_2 in female reproduction. H-PGDS and both DP_1 and $CRTH_2$ receptors are expressed in the placenta and L-PGDS is present in amniotic fluid, indicating a role in the regulation of placental communication (Lumsden *et al*. 1986, Saito *et al*. 2002). *H-Pgds* mRNA was localized in the granulosa cells from primary to pre-ovulatory follicles of the mouse adult ovary (Farhat *et al*. 2011). In this tissue, H-PGDS-induced PGD_2 interferes with FSH signaling through increased *Fshr* and *Lhcgr* (*LhR*) receptor expression, leading to the activation of steroidogenic *Cyp11a1* and *Star* gene expression, and subsequently to progesterone secretion. Furthermore, H-PGDS-induced PGD_2 is involved in the regulation of follicular growth through inhibition of granulosa cell proliferation in growing follicles (Farhat *et al*. 2011).

However, numerous roles of other PGs, PGE_2, $PGF_{2\alpha}$, and PGI_2 have been highlighted in different stages of blastocyst implantation: vascular permeabilization, stromal decidualization, blastocyst growth and development, leukocyte recruitment, embryo transport, trophoblast invasion, and extracellular matrix remodeling (Salleh 2014). The respective contribution of these PGs

in female reproduction was highlighted through the analysis of the *Cox1* and/or *Cox2*-knockout mice (Morita 2002). In particular, *Cox2* gene-deficient mice have defective ovulation, fertilization, and implantation mechanisms (Loftin *et al*. 2001). This phenotype was mimicked in $Ep2^{-/-}$ receptor mice, demonstrating the involvement of PGE_2 in these processes. COX2, PGE_2, and Ptger2, synthesized in follicular cumulus cells in response to gonadotropins, induce the follicle and oocyte maturation necessary for fertilization and ovulation (Kobayashi & Narumiya 2002). Furthermore, mice with targeted disruption of the *Cox1* gene have delayed parturition resulting in neonatal death, demonstrating the role of *Cox1* for the initiation of labor (Gross *et al*. 1998). $PGF_{2\alpha}$, which is highly expressed in the uterus, is involved in this process via the FP receptor. Moreover, $PGF_{2\alpha}$ expression in the corpus luteum of the ovary is also involved in the apoptosis of these cells in the absence of gestation (Hasumoto *et al*. 1997).

Male reproduction

In the male, $Cox1^{-/-}$ and $Cox2^{-/-}$ mouse models do not exhibit perturbed reproductive processes. However, *L-PGDS* is widely expressed in the testis and caput epididymis of bull and mouse models (Gerena *et al*. 2000*a*,*b*). L-PGDS is detected in bovine and human seminal plasma (Gerena *et al*. 1998, Tokugawa *et al*. 1998) and its concentration is lower in oligozoospermic than in normozoospermic men (Tokugawa *et al*. 1998), suggesting that this protein plays a role in both the development and maturation of sperm and emphasizes the role of L-PGDS in spermatogenesis. *L-Pgds* mRNA expression is found mainly in Leydig cells (Baker & O'Shaughnessy 2001), prospermatogonia, and SOX9-expressing Sertoli cells (Moniot *et al*. 2009) of the adult mouse testis. In rat, L-PGDS was detected in the Sertoli and germ cells of the adult testis (Samy *et al*. 2000). In humans, L-PGDS, H-PGDS, and DP_1 receptor are also expressed in the interstitial compartments of testes with normal and impaired spermatogenesis (Schell *et al*. 2007). L-PGDS and H-PGDS are expressed in Leydig cells and mast cells, respectively, along with COX2, in testes with impaired spermatogenesis. COX1 and COX2 are shown to be absent in normal human testes, whereas they are highly expressed in testicular cancer, and act to induce the growth of testicular cancer cells (Hase *et al*. 2003). The expression of COX2 in testicular biopsies from patients with mixed atrophy is correlated with H-PGDS expression in the mast cells of these testes (Welter *et al*. 2011). The major function of L-PGDS in spermatogenesis may be related with its role in the supply of retinoids, thyroid hormones, and essential fatty acids for the development of germ cells in the seminiferous tubules and maturing spermatozoa in the epididymides (Urade & Hayaishi 2000*a*). However, the role of L-PGDS in male reproduction remains unclear (Leone *et al*. 2002). H-PGDS expression in the male gonad is not well documented. The expression was detected in the Leydig cells and mast cells of the testes of human patients with impaired spermatogenesis (Schell *et al*. 2007) and in the germ cells of murine testes (personal data not shown); however, its role in reproduction is unknown.

15-Deoxy PGJ_2, a metabolite of PGD_2 influences the expression of differentiation markers (SMC, smooth muscle actin) and the contractibility of the human peritubular cells of the testes (Schell *et al*. 2010) and thus, may be involved in infertility (Welter *et al*. 2013). *COX2* mRNA expression was greatly increased in experimental cryptorchid testes, when compared with contralateral testes. Furthermore, in the spermatocytes of the cryptorchid testes the COX2 protein was specifically upregulated, thus protecting germ cells against apoptosis and disturbance of spermatogenesis (Kubota *et al*. 2011).

Furthermore, PGD_2 induced testosterone production in Leydig cells isolated from hamster testes (Schell *et al*. 2007). On the other hand, COX2 activity was shown to reduce steroidogenesis by decreasing *Star* gene expression in MA-10 mouse Leydig cells (Wang *et al*. 2003). However, the role of PGD_2 in the steroidogenesis process is still unclear because other reports using organotypic cultures of adult human gonads did not find a link between the effect of analgesics on PG synthesis and inhibition of testosterone production (Albert *et al*. 2013).

PGD_2 and the formation of embryonic male gonads

PGD_2 signaling components are expressed in embryonic testes

Amongst the male-enriched bands, identified by representational difference analysis (RDA) at embryonic stage E12.5, the gene encoding for L-PGDS was identified (Adams & McLaren 2002). The expression of *L-Pgds* mRNA in developing urogenital ridges was first detected in the Sertoli cells and prospermatogonia of late E11.5 male genital ridges (Adams & McLaren 2002). The expression of *L-Pgds* mRNAs in both somatic and germ cell compartments was confirmed at E13.5, although somatic expression was higher than that of germ cells (Moniot *et al*. 2014). *L-Pgds* showed similar expression profiles to *Sox9* and *Fgf9*, with expression starting at mid-late E11.5 and progressing to a plateau at E12.5 (Wilhelm *et al*. 2005). *L-Pgds* expression was described as a dynamic wave-like expression pattern, closely resembling that of *Sry* and *Sox9* in the embryonic testis. *L-Pgds* transcripts were detected in the center of the testis at the 17 tail somites (Ts) stage, shortly after the onset of *Sox9* expression at 15 Ts, and were shown to be upregulated at 21 Ts (Wilhelm *et al*. 2007). L-PGDS protein expression was evident in the E12.5 male gonads, in both the Sertoli and germ cells (Moniot *et al*. 2009). *L-Pgds* mRNA expression shifts from the

seminiferous tubules in the embryonic gonad and neonatal testis to the interstitial compartment, particularly the Leydig cells in the adult testis (Baker & O'Shaughnessy 2001, Moniot *et al.* 2009).

Concerning the second PGD_2-inducing H-Pgds enzyme, *H-Pgds* mRNA expression in both germ and somatic cells was found in E11.5–E17.5 gonads. In addition, the H-PGDS protein is also expressed in both cell types (Moniot *et al.* 2011, 2014). Production of PGD_2 by both the somatic and germ cell lineages was confirmed, using chemical fixation of PGD_2 on its production site (Bandeira-Melo *et al.* 2011) followed by immunofluorescence analysis, suggesting that both L-PGDS and H-PGDS enzyme capabilities are active within the embryonic gonad (Moniot *et al.* 2014). On the other hand, in the E13.5 male gonad, the DP_1 receptor is only expressed in somatic cells whereas the DP_2 is expressed in both germ cells and somatic compartments, at the mRNA and protein levels (Moniot *et al.* 2014).

PGD_2 signaling is involved in somatic differentiation

In most mammals, somatic sex determination in males is initiated in undifferentiated embryonic gonads by the expression of the *Sry* gene, which occurs at stages E10.5–E12.5 in mice, initiating testis differentiating *Sox9* gene expression (Sekido & Lovell-Badge 2008). The master effector gene *Sox9* encodes a transcription factor that belongs to the HMG superfamily (Wagner *et al.* 1994). Before sex determination and before the peak of *Sry* expression at E11.5, SOX9 is excluded from the nucleus in the genital ridge of both sexes (Morais da Silva *et al.* 1996, de Santa Barbara *et al.* 2000), via a nuclear export signal (NES), located in its HMG domain (Gasca *et al.* 2002), and is retained in the cytoplasm, possibly via its interaction with microtubules (Malki *et al.* 2005*a*). Upon sex determination, the SOX9 protein is transported into the nucleus in the male gonad. PGD_2 signaling via its DP_1 receptor and stimulation of the cAMP pathway induce SOX9 nuclear translocation via PKA phosphorylation in NT2/D1 cells (Malki *et al.* 2005*b*) (Fig. 2). Indeed, in *L-Pgds*$^{-/-}$ gonads, SOX9 subcellular localization and testis cord formation were impaired up to E13.5, even though a variable SOX9 expression pattern and sex cord formation phenotype, ranging from normal to severely abnormal, were found (Moniot *et al.* 2009). Furthermore, the PGD_2-producing H-PGDS enzyme is expressed in the embryonic gonad at mid E11.5 (16–17 Ts), despite L-PGDS not being expressed. Inhibition of H-Pgds enzymatic activity by the specific HQL-79 inhibitor impairs nuclear translocation of the SOX9 protein in E11.5 pre-Sertoli cells, a phenotype that was also found in *H-Pgds*$^{-/-}$ XY gonads (Moniot *et al.* 2011), suggesting that an initial H-PGDS-mediated PGD_2 signal could participate in the SOX9 nuclear translocation necessary for the process of Sertoli cell differentiation (Fig. 2).

Moreover, PGD_2 has a masculinizing effect on cultivated XX gonadal explants (ectopic testicular cord formation and expression of AMH) (Adams & McLaren 2002) through the stimulation of *Sox9* gene expression (Wilhelm *et al.* 2005), as SOX9 can directly bind to and activate the *L-Pgds* promoter (Wilhelm *et al.* 2007). *L-Pgds* expression was indeed abolished in E12.0 male *Sox9*$^{-/-}$ gonads (*Ck19*-Cre; *Sox9*$^{flox/flox}$ mice), confirming that SOX9 is required for the initiation of *L-Pgds* gene expression, as *L-Pgds* is a direct target gene for SOX9. Moreover, ablation of *Sox9* after the onset of *L-Pgds* expression (E13.5–E14.5 *Amh*-Cre; *Sox9*$^{flox/flox}$) also induces a strong downregulation of *L-Pgds* expression, demonstrating the requirement for the SOX9 protein in the maintenance of *L-Pgds* gene expression in embryonic Sertoli cells (Moniot *et al.* 2009). Altogether, these data show that *L-Pgds* and *Sox9* genes are part of a regulatory loop, initiating and maintaining *L-Pgds* expression and upregulating *Sox9*. This regulatory loop is independent on the fibroblast growth factor 9 (*Fgf9*)/*Sox9* regulatory loop previously identified (Kim *et al.* 2006). Indeed, the onset of *L-Pgds* expression was not affected in *Fgf9*$^{-/-}$ (Moniot *et al.* 2009) or Fgf9 receptor R2 (*FgfR2*$^{-/-}$) (Kim *et al.* 2007) mutant XY gonads and *Fgf9* mRNA expression was not modified in E12.5 *L-Pgds*$^{-/-}$ gonads, confirming that both pathways do not interact genetically. However, both FGF9 and PGD_2 signaling molecules cooperate to additively upregulate *Sox9* expression in the Sertoli-like NT2D1 cell line (Moniot *et al.* 2009; Fig. 2). Many endocrine disruptors (phtalates, bisphenol) and several NSAIDS that inhibit COX activities reduce PGD_2 production in the SC5 mouse Sertoli cell line and in cultured rat fetal testes (Kristensen *et al.* 2011*a*,*b*, 2012), leading to reduced testosterone production. However, the role of PGD_2 in the onset of the steroidogenesis process remains unclear. Unlike adult human or rat testes, *ex vivo* exposure of embryonic human testis to paracetamol, aspirin, and indomethacin has no effect either on the production of PGD_2 or on the concentration of testosterone (Mazaud-Guittot *et al.* 2013).

PGD_2 is also involved in the process of testicular descent in mice, because adult *L-Pgds*$^{-/-}$ mice present unilateral cryptorchidism without impaired androgen signaling, but rather a decrease in the INSL3 receptor *Rxfp2* mRNA expression in the gubernaculum (Philibert *et al.* 2013). The use of NSAIDS, which inhibit COXs enzymes, during the second trimester of pregnancy is associated with an increased risk of cryptorchidism in humans (Jensen *et al.* 2010, Kristensen *et al.* 2011*a*); however, the nature of the PG(s) involved in this phenotype is unknown.

PGD_2 signaling is involved in germ line differentiation

The differentiated Sertoli cells will then influence the germ cell lineage to differentiate (Svingen & Koopman 2013).

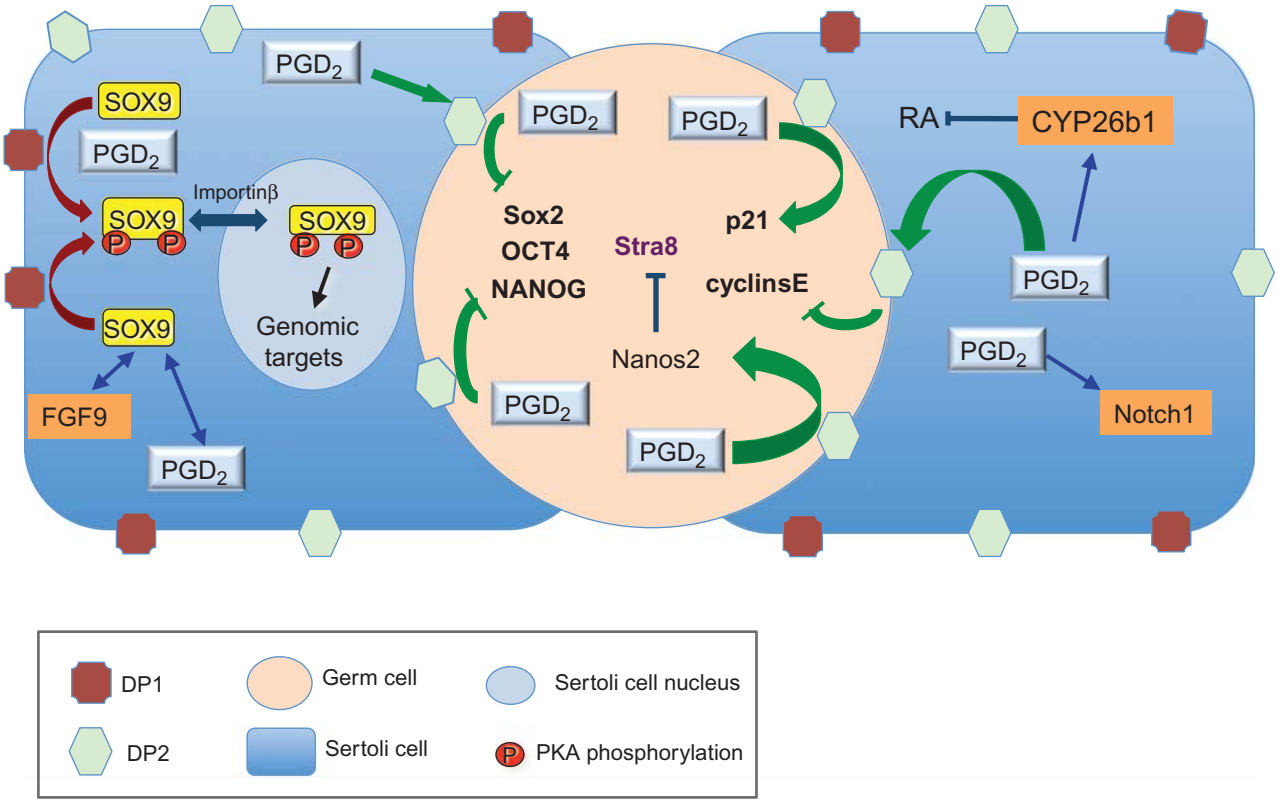

Figure 2 Model for the role of PGD_2 signaling in Sertoli cell and germ cell differentiation in the male embryonic gonad. Upon sex determination around E11.5, the Sertoli cell differentiating factor SOX9 is transported into the nucleus in the male gonad. PGD_2 signaling via its DP_1 receptor and stimulation of the cAMP pathway induces SOX9 nuclear translocation via protein kinase A (PKA) phosphorylation. PGD_2 signaling through *L-Pgds* is part of a regulatory loop between *L-Pgds* and *Sox9* genes, which acts independently of the FGF9/SOX9 loop. Later around E13.5, PGD_2 signaling, which is produced by both the Sertoli cell and germ cells, is involved in the germline differentiation, through its DP_2 receptor. PGD_2 is involved in the activation of the male germ cell marker *Nanos2*, inhibiting meiosis through the repression of *Stra8*; PGD_2 is also involved in the activation of the cell cycle inhibitor p21 expression and the repression of Cyclins E expression, and in the repression of the pluripotent markers expression *Sox2*, *Pou5f1*, and *Nanog*, contributing to the mitotic arrest of the male germline. On the other hand, PGD_2 produced in Sertoli cells activates *Notch1* and *Cyp26B1* gene expression, indirectly influencing the germ cell fate.

In mice, primordial germ cells (PGCs) colonize the genital ridge at around E10.5 and continue proliferating until E13.5 (McLaren 2000). At this time, in the developing ovary, germ cells enter prophase of the first meiotic division after the upregulation of the pre-meiotic gene *Stra8* (Ewen & Koopman 2010). In contrast, in the testis, germ cells stop proliferating and fully enter the G_0/G_1 phase of the cell cycle by E15.5 (Western *et al.* 2008); meanwhile, pluripotent marker expression is repressed (Western *et al.* 2010) and male germ cell markers such as *Nanos2* are upregulated, which actively inhibits meiosis entry and thus contributes to the differentiation of the germline (Suzuki & Saga 2008). Male germ cells remain quiescent until shortly after birth, at which point they resume mitosis and then initiate meiosis around 8 days *post partum* (dpp) (Ewen & Koopman 2010).

In vivo analysis of double-knockout *L/H-Pgds* (*L/H-Pgds*$^{-/-}$, i.e. depleted for PGD_2) gonads showed that the proliferation rate of E13.5 mutant germ cells increased by 1.5-fold compared with WT germ cells. At E15.5 and even E17.5, nearly 10% of the mutant germ cells were still Ki-67 positive, showing that a significant proportion of the mutant germ cells were not mitotically arrested and were still engaged in the cell cycle at a time which should be quiescent (Moniot *et al.* 2014). Meanwhile, cell cycle inhibitors $p21^{Cip1}$ and $p57^{Kip2}$ are downregulated and cell cycle activators *CyclinE1* and *E2* are upregulated (Fig. 2), suggesting that PGD_2 signaling is involved in the control of cell cycle genes in fetal testes, contributing to the arrest of mitotic process. Moreover, at late embryonic stages, the ectopic expression of pluripotency markers *Pou5f1* (*Oct4*), *Sox2*, and *Nanog* was detected in *L/H-Pgds*$^{-/-}$ testes and the male germ cell marker *Nanos2* is downregulated in mutant testes suggesting that PGD_2 has a role in the germ cell differentiation in the embryonic testis. Somatic factors, *Notch1* (Garcia *et al.* 2013) and Cyp26B1, an RA-metabolizing enzyme of the cytochrome P450 family that is produced by the Sertoli cells and that protects germ cells from RA (Bowles *et al.* 2006), were significantly reduced in E13.5 mutant gonads (Fig. 2), suggesting that PGD_2 produced by

Sertoli cells influences the differentiation of the embryonic germ cells (Moniot *et al*. 2014). Finally, the DP2 receptor is responsive to the effects of PGD_2 in the male germline, because *Dp2*$^{-/-}$ testes have the same phenotype as that of the *L/H-Pgds*$^{-/-}$ testes (Fig. 2; Moniot *et al*. 2014). PGD_2 signaling is thus an early pathway acting in both paracrine and autocrine manners (Fig. 2), contributing to the proper differentiation of male fetal germ cells.

Conclusions, perspectives

The development and maturation of the reproductive organs are complex and highly regulated biological mechanisms, in which numerous factors and signaling pathways are involved. In this review, we addressed the advancement of knowledge on PGD_2 signaling in female and male reproduction, particularly in the formation of embryonic gonads and the maturation of adult reproductive organs. Whereas PGD_2 signaling through both PGDSs is involved in the differentiation of the embryonic testis at the somatic and germ cell levels, its roles in steroidogenesis and spermatogenesis in adults are still under debate. The dual roles of the L-PGDS enzyme suggest that this protein plays a role in both the development and maturation of sperm and spermatogenesis. Seminal L-PGDS, an important carrier of bile pigments, retinoids, thyroid hormones, and essential fatty acids, would contribute to providing, beyond the blood–testis barrier, thyroid hormones, and retinoids to the developing germ cells in the seminiferous tubules and the maturing spermatozoa in the epididymis. Both PGDSs are indeed expressed in testes of patients with impaired spermatogenesis, suggesting their involvement in fertility (Leone *et al*. 2002).

The increasing incidence of disorders of the reproductive organs in men, such as cryptorchidism, hypospadia, decreased semen quality, and testosterone concentration, or testicular cancers, has been observed in recent decades (Toppari *et al*. 1996, Skakkebaek *et al*. 2001). The use of NSAIDS drugs during the second trimester of pregnancy is associated with an increased risk of cryptorchidism in humans (Jensen *et al*. 2010) and in rats (Kristensen *et al*. 2011*a*). As PGD_2 is a potential target for endocrine disruptors and NSAIDs, our findings thus open new perspectives for future investigations into how germ cell development can be perturbed by the external environment. Germ cells that are not controlled appropriately during fetal life can later transform into carcinoma *in situ* (CIS), the pluripotent precursor cells for testicular germ cell tumors (Kristensen *et al*. 2008). Indeed, PGD_2/DP_2 signaling is involved in the control of key regulators of the G_1/S phase checkpoint and in the repression of pluripotent markers' expression in the male embryonic germline; its ablation resulting in CIS-like phenotype in the mice gonad. Further work will determine whether the double *L/H-Pgds* mutation can lead to a high incidence of germ-line tumors in the 129sv background. PGD_2 signaling through L-PGDS and SOX9 expression suppresses NT2/D1 cell migration and invasion, suggesting an important role for PGD_2 in cancer cell suppression in the testis (Wu *et al*. 2012). L-PGDS is abnormally expressed in ovarian tumors (Su *et al*. 2003, Malki *et al*. 2007). The antiproliferative effect of PGD_2 has been highlighted in human ovarian cancer cell lines (Kikuchi *et al*. 1986, Su *et al*. 2003); stimulation of the PGD_2/DP_1 signal transduction pathway upregulates SOX9 expression leading to the inhibition of cancer cells growth (Malki *et al*. 2007).

The recent findings, showing that endocrine disruptors and NSAIDS influence the PGD_2 production in the testes and that PGD_2 signaling is involved in multiples steps of the embryonic testis differentiation, might introduce this pathway in the etiology of the reproduction diseases. As the pharmacology of the PGD_2 signaling is well documented, either activators of this pathway or DP_1/DP_2 agonists may be useful as new therapeutic agents.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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