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Prostaglandin D_2 synthase related to estrogen in the female reproductive tract

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ABSTRACT

Prostaglandin D_2 synthase (PTGDS), also known as a glutathione-independent prostaglandin D synthase, catalyzes prostaglandin H_2 to prostaglandin D_2 that exhibits functions that include regulation of the central nervous system, contraction/relaxation of smooth muscle and inhibition of platelet aggregation. Gene profiling data based on our previous study indicated that PTGDS is significantly increased during development, differentiation and remodeling of the oviduct in chickens in response to estrogen. Therefore, the aims of the present study were to investigate expression of PTGDS in the oviduct and examine if the relationship between PTGDS and estrogen is conserved during development and remodeling of the oviduct. Results of our study indicate d that *PTGDS* expression is specifically localized to the luminal (LE) and glandular epithelial (GE) cells of the chicken oviduct in response to diethylstilbestrol, a synthetic estrogen. In addition, *PTGDS* expression increased during the regeneration phase of the oviduct in concert with increasing concentrations of estrogen in the circulation of laying hens during induced molting. Moreover, PTGDS mRNA and protein were expressed abundantly in GE of ovarian carcinoma, but not in normal ovaries. These results provide the first evidence that *PTGDS* is a novel estrogen-stimulated gene in oviductal epithelial cells, as well as a candidate biomarker for diagnosis of ovarian carcinoma.

1. Introduction

As a metabolite of arachidonic acid, prostaglandin H_2 is converted to prostaglandin D_2 by prostaglandin D synthases including hematopoietic prostaglandin synthase (HPGDS) and lipocalin-type prostaglandin synthase (PTGDS) [1]. HPGDS was first isolated from rat spleen [2] and its expression was most abundant in liver, kidney, small intestine, and colon in female chickens [3]. PTGDS was first isolated and identified in the rat brain and it catalyzes conversion of prostaglandin H_2 into prostaglandin D_2 in the central nervous system and genital organs [4]. PTGDS was the first member of the lipocalin family including small secretory proteins that transport lipophilic molecules with high structural homology to lipocalin proteins [5]. Thus, PTGDS is considered a bi-functional protein serving as a prostaglandin D_2 generating enzyme and a lipophilic molecule transporter [6]. In general, PTGDS is synthesized and secreted by cells of the central nervous system, but also highly expressed by cells in the genital organs. For example, *Ptgds* is involved in differentiation of Sertoli cells during development of the male gonads in mice [7]. Recently, Moniot and colleagues reported the pattern of PTGDS expression during gonadal and testicular differentiation in chicks [8]. However, little is known about *PTGDS* gene expression in the female reproductive tract. Our previous gene profiling data using a chicken DNA microarray analyses indicated that expression of the *PTGDS* gene increased with increases in circulating concentrations of estrogen in plasma of laying hens during the recrudescence phase of oviduct remodeling following diet-induced molting in laying hens [9]. In that study, circulating concentrations of estrogen decreased during regression of the ovary and oviduct during feeding a high zinc diet to laying hens and then concentrations of estrogen increased in blood after feeding of a normal commercial diet resumed and recrudescence of the ovaries and oviduct occurred. Therefore, the hypothesis investigated in this study was that PTGDS plays important roles in the development and differentiation of the oviduct in response to estrogen in chicks and in laying hens. The objectives of the present study were to: (1) evaluate tissue- and cell-specific expression of PTGDS in the female reproductive organs of chickens; (2)

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determine whether PTGDS expression is regulated by estrogen during development of the chick oviduct; (3) determine whether PTGDS expression is regulated by estrogen during regression and recrudescence phases of induced molting in laying hens; and (4) compare differential expression patterns for PTGDS in normal and cancerous ovaries of laying hens. Our results provide the first evidence that PTGDS has essential roles in development and differentiation of the oviduct of laying hens in an estrogen-dependent manner and that it may be a candidate biomarker gene for diagnosis of epithelial cell-derived ovarian carcinogenesis in laying hens and women.

2. Materials and methods

2.1. Experimental animals and animal care

The experimental use of chickens for this study was approved by the Animal Care and Use Committee of Korea University. All chickens were exposed to a light regimen of 15 h light and 9 h dark with *ad libitum* access to feed and water, and subjected to standard poultry husbandry guidelines.

2.2. Tissue samples

2.2.1. Study one

Female chicks were identified by PCR analysis using W chromosome-specific primer sets. Treatment with DES and recovery of the oviduct ($n = 5$) were conducted as reported previously [10,11].

2.2.2. Study two

Hens ($n = 5$ per time point) in each subgroup including the molting group (normal feeding group, 6 days and 12 days after onset of zinc feeding) and the recrudescence group (20, 25, 30 or 35 days after onset of zinc feeding, and 8, 13, 18 or 23 days of normal feeding after cessation of egg production and removal from the high zinc diet) were euthanized using 60–70% carbon dioxide prior to collecting the oviduct on each assigned day [9].

2.2.3. Study three

A total 136 laying hens (88 aged over 36 months and 48 aged over 24 months), which had completely stopped laying eggs were euthanized for biopsy and collection of cancerous ($n = 10$) ovaries. As a control, normal ($n = 5$) ovaries were also collected from egg-laying hens. We examined the tumor stage in 10 hens with using characteristic features of chicken ovarian cancer [12,13].

2.3. RNA isolation

Total cellular RNA was isolated from frozen tissues using Trizol reagent (Invitrogen, Carlsbad, CA) according to manufacturer's recommendations.

2.4. Quantitative RT-PCR analysis

The level of expression of *PTGDS* mRNA in the chicken oviducts and ovaries was assessed using quantitative RT-PCR as described previously [14].

2.5. In situ hybridization analysis

Location of *PTGDS* mRNA in sections (5 μm) of chicken oviducts and ovaries was determined by *in situ* hybridization analysis as described previously [14].

2.6. Immunohistochemistry

Immunocytochemical localization of PTGDS protein was performed as described previously using a rabbit polyclonal antibody to PTGDS (catalog number: sc-30067, Santa Cruz Biotechnology, Inc., Dallas, TX) at a final dilution of 1:500 (0.4 μg/ml). Antigen retrieval was performed using the boiling citrate method as described previously [15].

2.7. Statistical analyses

Data presented for quantitative PCR analysis are expressed as mean ± SEM unless otherwise stated. Differences in the variances between normal and cancerous ovaries were analyzed using the F test, and differences between means were subjected to the Student's t test. Differences with a probability value of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Estrogen regulates PTGDS gene expression during the development of the chicken oviduct

As illustrated in Fig. 1A, *PTGDS* mRNA increased 6-fold ($P < 0.001$) in the oviduct of DES-treated chicks as compared to non-treated chicks. Especially, *PTGDS* mRNA increased 47-fold ($P < 0.001$) in the magnum of DES-treated chicks, but not in other sections of the DES treated oviducts (Fig. 1B). To investigate localization of PTGDS mRNA and protein, *in situ* hybridization and immunohistochemical analyses were performed. As shown in Fig. 1C, *PTGDS* mRNA was expressed abundantly in luminal (LE) and glandular epithelia (GE) of the oviductal magnum of DES treated chicks, but not in any other sections of the oviduct of DES treated or non-treated chicks. Consistent with these results, immunoreactive PTGDS protein was most abundant in the magnum of DES treated chicks (Fig. 1D). Non-specific rabbit IgG, used as a negative control, did not detect immunoreactive PTGDS protein in any cell-type chick oviducts.

3.2. Estrogen regulates PTGDS expression in the magnum of the oviducts of laying hens during the period of induced molting

Gene profiling in the previous study [9] revealed that *PTGDS* expression decreased 60% in the oviduct at Day 12 as compared with Day 0 whereas it increased 5.6-fold in the oviduct on Day 35 as compared to Day 12 of the period of recrudescence of the oviduct. In accordance with results of the previous study [9], we examined effects of varying concentrations of estrogen in blood on expression of PTGDS during the regression and recrudescence phases of the diet-induced molting period. As illustrated in Fig. 2A and B, *PTGDS* mRNA expression decreased sharply between Days 6 and 20 (regression phase of molting) and then increased significantly between Days 30 and 35 (recrudescence phase of molting period) of the molting period. *In situ* hybridization analysis revealed that *PTGDS* mRNA was localized predominantly to GE of the magnum during the recrudescence phase of induced molting (Fig. 2C), and PTGDS protein was abundant in LE and GE of the magnum during the recrudescence phase of induced molting (Fig. 2D).

3.3. Distinct expression patterns of PTGDS in normal and cancerous ovaries of laying hens

We determined cell-specific expression of PTGDS in ovarian cancer in 96-week-old laying hens. As illustrated in Fig. 3A,

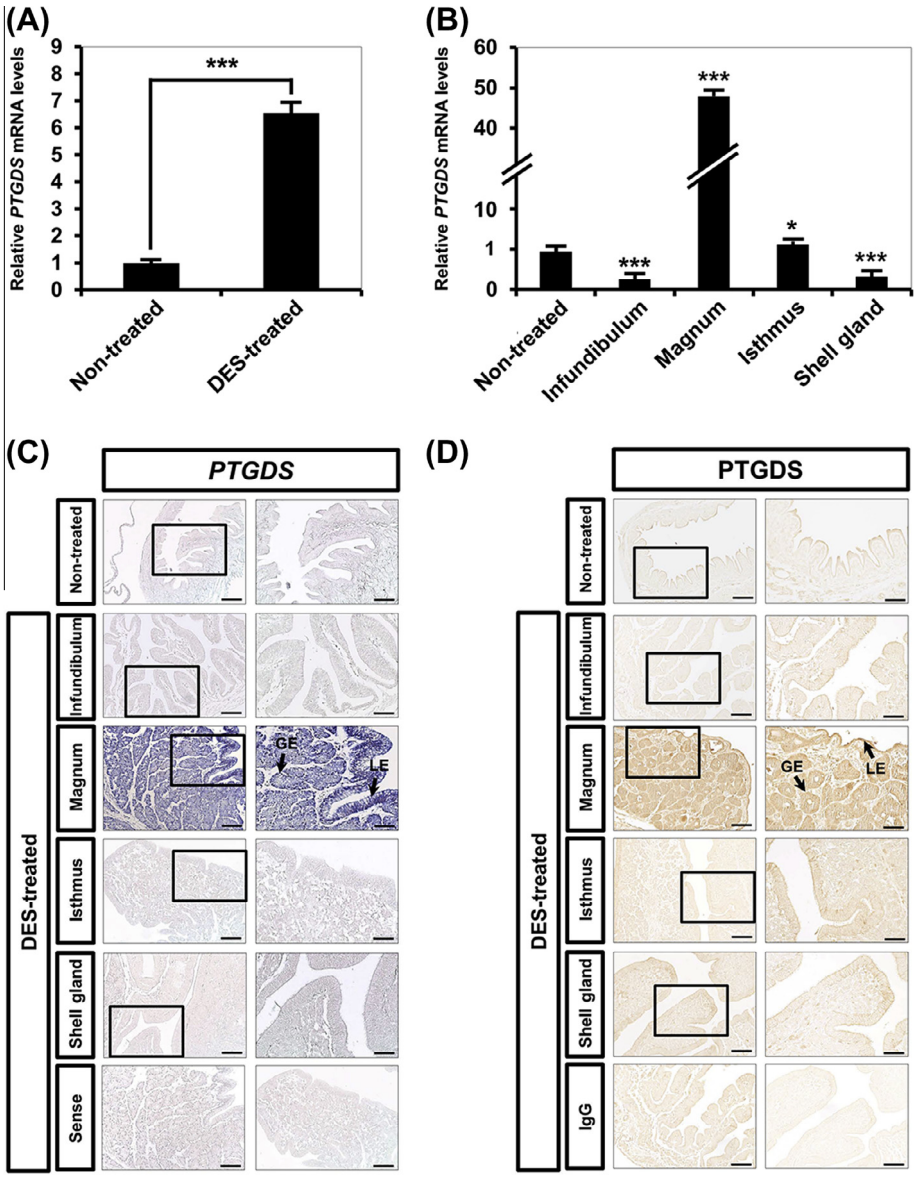

Fig. 1. Effects of DES on tissue- and cell-specific expression PTGDS in chicken oviduct. (A and B) Quantitative-PCR analyses were performed using cDNA templates from non-treated chicken and the four segments of the chicken oviduct (infundibulum, magnum, isthmus, and shell gland) of DES-treated oviducts (mean ± SEM; $^{***}P < 0.001$). These experiments were conducted in triplicate and normalized to control *GAPDH* expression. (C and D) *In situ* hybridization and immunohistochemical analyses indicated localization of PTGDS mRNA and protein, respectively in oviducts of DES-treated and non-treated chicks. Cross-sections of the four segments treated with DES or vehicle were hybridized with antisense or sense chicken *PTGDS* cRNA probes (C). For the IgG control, normal rabbit IgG was substituted for the primary antibody. Sections were not counterstained (D). Legend: LE, luminal epithelium; GE, glandular epithelium; *Scale bar* represents 50 μm (the first columnar panels and 20 μm (the second columnar panels).

quantitative PCR revealed that *PTGDS* mRNA increased 2- ($P < 0.01$) and 5-fold ($P < 0.01$) in cancerous ovaries as compared with normal ovaries of laying hens between 48 and 96 weeks of age, respectively. Additionally, *PTGDS* mRNA localized predominantly to GE of cancerous and normal ovaries, but not other cell-types including stroma and blood vessels (Fig. 3B). Consistent with these results, PTGDS protein was only detected in GE of cancerous ovaries (Fig. 3C).

4. Discussion

Results of this study provide evidence that PTGDS is expressed in the magnum of the reproductive tracts of female chickens in an estrogen-dependent manner. In addition, results of the present study provide the first evidence for stimulation of PTGDS expression in ovarian carcinomas as compared to normal ovarian tissue in laying hens. Therefore, our results strongly support our hypothesis that PTGDS plays essential roles in growth, differentiation and remodeling of the oviduct in chickens and that PTGDS expression is in response to estrogen and that it may be involved in the pathogenesis of ovarian carcinogenesis in laying hens.

Prostaglandin D_2 is involved in various physiological processes including regulation of sleep [16], smooth muscle contraction [17], platelet aggregation [18], bronchoconstriction [19], and inflammatory cells [20]. Also, in female reproduction, PGD_2 is secreted from endometrium and myometrium in greater amounts [21]. Prostaglandin endoperoxidase synthase 1 or 2 (PTGS1 and PTGS2) converts arachidonic acid to PGH_2 which is converted by prostaglandin D synthases HPGDS and PTGDS to PGD_2 [22]. As a cytosolic enzyme, HPGDS is involved in immune response as it is expressed by inflammatory cells including mast cells,

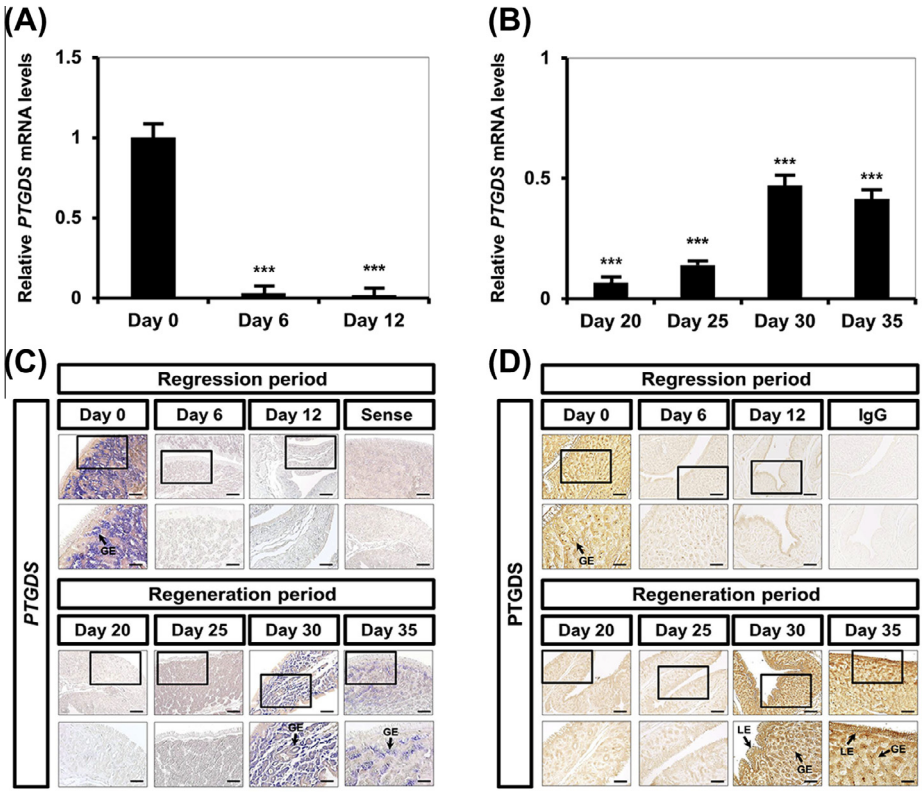

Fig. 2. Quantitation of *PTGDS* mRNA during regression and recrudescence of magnum of hens during induced molting. (A and B) Quantitative RT-PCR was conducted using cDNA templates from the magnum of hens fed a control diet (Day 0), zinc fed hens in which the oviduct was regressing (Days 6 and 12) (A), and hens in which the oviduct was undergoing recrudescence (Days 20, 25, 30, and 35) (B). These experiments were performed in triplicate and normalized to control *GAPDH* expression. The asterisks denote statistically significant differences (mean ± SEM; $^{***}P < 0.001$). (C and D) The localization of PTGDS mRNA and protein in the oviduct of hens on different days of the pre- and post-molting periods was analyzed by *in situ* hybridization (C) and immunohistochemistry (D). Legend: LE, luminal epithelium; GE, glandular epithelium; *Scale bar* represents 50 μm (the first and third horizontal panels) and 20 μm (the second and fourth horizontal panels).

antigen-presenting cells, and Th2 cells in mammals. HPGDS is also abundant in liver, kidney, small intestine and colon, but only weakly detectable in spleen, thymus, heart, and brain of chickens [3]. Recently, Urade and colleagues identified the chicken *PTGDS* gene on chromosome 17 that has six exons encoding for 185 amino acids (20.8-kDa) [23]. PTGDS, a member of the lipocalin gene family, has highly conserved primary structure such as eight beta-strands and one alpha-helix and mainly transports lipophilic molecules [5]. Thus, as a unique dual-function protein, PTGDS acts as a prostaglandin D_2-producing enzyme as well as a lipophilic molecule transporter [6]. Recently, Ragolia and colleagues reported accelerated cardiovascular disease, diabetic nephropathy, insulin resistance, and impaired glucose tolerance in *Ptgds*$^{-/-}$ mice and further dysregulation of *PTGDS* gene expression stimulated glucose transport through enhanced GLUT4 translocation [24,25]. On the other hand, during embryo development, the *PTGDS* gene is expressed only in the urogenital ridge of males along with SOX9, but it is not expressed in the female chick during the early embryonic stages [8]. These results indicated that the *PTGDS* gene is a male specific gene involved in gonadal differentiation to complete formation of Sertoli. In addition, the *PTGDS* gene is highly expressed in brain, lung, and kidney, and moderately expressed in heart and liver of neonatal chicks. And, expression of PTGDS is strong in brain, heart, lung, skeletal muscle, and ovary but, weak in intestine and testes of adult chickens [23]. However, expression of PTGDS in the chicken oviduct has not been reported.

In the present study, we determined cell-type specific PTGDS expression in each section of the chicken oviduct. The oviduct of laying hens is well known as an excellent model for study of basic mechanisms of organogenesis in developmental biology. For instance, it is very suitable for investigating morphological changes as well as biochemical/physiological effects on development and cytodifferentiation of reproductive tracts of mammalian and non-mammalian species in response to ovarian steroid hormones [11]. Among them, estrogen is the primary sex steroid hormone that plays indispensable roles in cell proliferation and differentiation of tubular glands and production of egg white proteins in the developing oviduct of laying hens [26]. Results of the present study demonstrated that estrogen stimulates PTGDS in the LE and GE of the magnum during growth, development, and differentiation of the chicken oviduct. Moreover, gene profiling data from our other study indicated that PTGDS is a candidate gene regulated by estrogen involved in regulatory mechanism(s) for regression and recrudescence of the oviduct of laying hens during induced molting.

Our current results demonstrate that expression of PTGDS mRNA and protein decreases ($P < 0.001$) during the induced molting period (Days 0–20) and increases ($P < 0.001$) during the recrudescence period (Days 25–35) with these changes being coordinate with changes in circulating concentrations of estradiol. There are some reports that support our findings. For example, in the nervous system of rodents, estrogen regulates PTGDS expression in hypothalamic nuclei and in the ventrolateral preoptic area after treatment with exogenous estrogen [27]. Indeed, expression of the *PTGDS* gene is regulated through some nuclear receptors, including the thyroid hormone receptor, glucocorticoid receptor, and estrogen receptor [23]. Collectively, these results suggested that PTGDS is a novel estrogen-stimulated gene involved in the

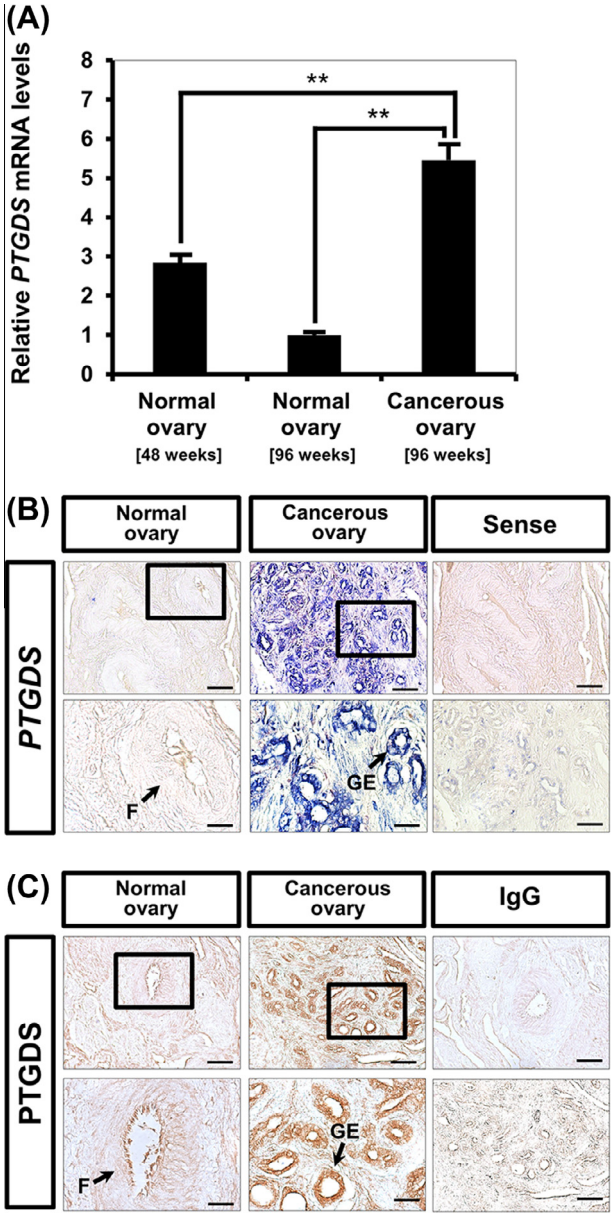

Fig. 3. Distribution and localization of PTGDS mRNA and protein in normal and cancerous ovaries from laying hens. (A) Quantitative PCR was conducted using cDNA templates from normal and cancerous ovaries of laying hens. These experiments were performed in triplicate and normalized to control *GAPDH* expression. The asterisks denote statistically significant differences (mean ± SEM; $^{**}P < 0.01$). (B) *In situ* hybridization analyses indicated cell-specific localization of *PTGDS* mRNA in normal and cancerous ovaries from hens. (C) Immunoreactive PTGDS protein in normal and cancerous ovaries from hens. For the IgG control, normal rabbit IgG was substituted for the primary antibody. Sections were not counterstained. Legend: F, follicle; GE, glandular epithelium. *Scale bar* represents 50 μm (the first horizontal panels in (B) and (C)) and 200 μm (the second horizontal panels in (B) and (C)).

development and cytodifferentiation of the immature chick oviduct, as well as remodeling/regeneration of the oviduct in response to estrogen during the period of molting in laying hens.

Epithelial cell-derived ovarian cancer (EOC) may arise from the distal oviduct of laying hens and many oviduct-associated genes are up-regulated in EOC by dysregulated estrogen levels [28]. Unfortunately, there are no or few symptoms and diagnostic biomarkers to detect early stage EOC in spite of the fact that it is the most common cause of cancer-related deaths among women [29,30]. Notwithstanding many attempts to develop adequate animal models for EOC research to discover effective biomarkers for early detection of the disease, there are few appropriate animal models due to very dissimilar physiological and pathological characteristics between experimental animals and women. Interestingly, the merits of the laying hen model are being recognized because mechanisms for progression of EOC and histological/pathological features are similar to EOC in women [12,31,32]. Indeed, we have reported several estrogen-stimulated genes that are expressed in GE of ovarian adenocarcinomas, but not normal ovaries from laying hens and these include *cathepsin B* (*CTSB*) [33], *serpin peptidase inhibitor, clade B, member 11* (*SERPINB11*) [13], *beta-defensin 11 (AvBD-11)* [34], and several cell cycle genes [35]. Although Fujimori and colleagues detected PTGDS expression in the ovaries of 24-week-old chickens [23], ovarian carcinoma generally occurs in laying hens that are 4- to 5-years of age. In the present study, PTGDS mRNA and protein are most abundant in GE in all cancerous ovarian tissues. The dysregulation of glandular structure is one of the most common features of ovarian carcinomas in both laying hens and women [12,36]. Previous studies have shown that PTGDS is involved in carcinogenesis in brain [37] and breast [38], as well as ovaries from women where it has been proposed to regulate cell proliferation and differentiation [39]. In addition, expression of *PTGDS* mRNA has been detected in various types of ovarian cancer cell lines [39,40]. Results of the present study suggest that over-expression of PTGDS is associated with progression of EOC in laying hens, and that it is a potential biomarker for early diagnosis of EOC in women.

Collectively, our present results indicate that expression of PTGDS is correlated with circulating concentrations of estrogen during development, remodeling, and differentiation of the chicken oviduct and in remodeling of the oviduct of laying hens during the molting period. Furthermore, PTGDS is clearly associated with abnormal development and dysfunction of ovarian tumors. Therefore, results of the current study provide new insights into novel functions of PTGDS as a regulatory factor in female reproductive organs and the possibility of serving as a biomarker for early detection of EOC in laying hens and women.

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