

# Von Hippel-Lindau gene expression on the human fallopian tube epithelium during the menstrual cycle

YAN-YAN LU, WEI-JIE ZHU and BAO-GUO XIE

Department of Developmental and Regenerative Biology, College of Life Science and Technology,  
Jinan University, Guangzhou, Guangdong 510632, P.R. China

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**Abstract.** The Von Hippel-Lindau gene (*VHL*) is a tumor suppressor gene, which is widely expressed in kidney, lung, breast, ovary, and cervix. *VHL* gene mutations can induce VHL disease and tumorigenesis. However, whether this gene is expressed in the human fallopian tube has not been evaluated. The objectives of this study were to investigate whether the *VHL* gene is expressed in human fallopian tube, and to investigate its expression changes during the menstrual cycle. Twenty-seven patients undergoing abdominal hysterectomy with adnexectomy for benign uterine disease were enrolled in the study. Human fallopian tubes were divided into proliferative stage (n=14) and secretory stage (n=13) according to the stage of the menstrual cycle they were isolated from. The expression of the *VHL* gene and protein was studied by reverse transcription-polymerase chain reaction (RT-PCR), western blotting and immunohistochemistry, respectively. The results revealed positive expression of the *VHL* protein in the cytoplasm of ciliated cells of the human fallopian tube. The mRNA and protein expression of *VHL* in the fallopian tubes was higher in the proliferative compared to the secretory phase of the menstrual cycle, but this difference was not significant ( $P>0.05$ ). Overall, this study presents data on the *VHL* mRNA and protein expression in the human fallopian tube, which may be relevant to the process of differentiation of ciliated and secretory cells.

## Introduction

The fallopian tube is the tubular organ connecting the periovarian space to the uterus, and performs several interrelated functions. It captures the cumulus-oocyte complex, maintains viability, and constrain the spermatozoa to the fertilization site.

Moreover, it provides the biological environment for fertilization, contributes to removal or addition of oocyte coatings, and nourishes the egg (1).

The Von Hippel-Lindau gene (*VHL*) was isolated by positional cloning and identified as a tumor suppressor gene since 1993 (2). *VHL*, which is a classical tumor suppressor gene, can regulate the mRNA stability of a number of target genes through selective degradation of RNA-bound proteins, including the endothelial growth factor (EGF), transforming growth factor- $\alpha$  (TGF- $\alpha$ ), hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ), and carbonic anhydrase 9 (3,4). *VHL* disease is an inherited neoplastic disease characterized by a predisposition to develop vascularized tumors or cysts in numerous tissues (5). Moreover, mutations in the *VHL* gene are associated with cancer development of a number of organs, including kidney, lung, breast, ovary, and cervix (6). The *VHL* protein (pVHL) has been ascribed several distinct biochemical activities, and was shown to be involved in the regulation of the cell cycle (7). pVHL is a multifunctional protein, related to the inhibition of cell growth, angiogenesis, fibronectin matrix assembly, activation of p53, and proteolysis; nearly all these processes contribute to its tumor suppressor function (8). In addition, pVHL is also a component of the mechanism that transduces local differences in oxygen tension at the fetal-maternal interface to the cytotrophoblasts, affecting their biologic behavior (9). However, whether the *VHL* gene is expressed in the human fallopian tube is presently unclear.

This study was carried out to investigate the expression of *VHL* at the mRNA and protein level in human healthy fallopian tube samples, isolated from the proliferative and the secretory stages of the menstrual cycle, and to elucidate whether *VHL* expression levels change during the different stages of the menstrual cycle.

## Materials and methods

**Tissue samples.** Samples of human healthy fallopian tube tissues were obtained by abdominal hysterectomy with salpingectomy for benign uterine disease. Twenty-seven fresh tissue samples of the proliferative (n=14) and the secretory phase (n=13) of the menstrual cycle were collected. One part of each sample was immediately frozen in liquid nitrogen or stored at -80°C until further use for reverse transcription-polymerase chain reaction (RT-PCR) and western blotting. The other part of the

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*Correspondence to:* Professor Wei-Jie Zhu, Department of Developmental and Regenerative Biology, College of Life Science and Technology, Jinan University, 601 Huang Pu Da Dao Xi, Guangzhou, Guangdong 510632, P.R. China  
E-mail: tzhujw@jnu.edu.cn

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samples was fixed in 10% formalin and embedded in paraffin for immunohistochemistry (IHC) analysis.

Patients with healthy fallopian tube tissues were operated for reasons unrelated to tubal dysfunction, and their mean  $\pm$  standard deviation (SD) age was 36 (4.38) years (range, 32-43 years). Their menstrual day was coincident with the histological diagnosis of the stage of the endometrium according to the criteria of Noyes *et al.* (10). Patients were excluded if they had received exogenous steroid treatment or chemotherapy within the last 6 months before surgery. All patients signed informed consent letters, and the study protocol was approved by the Local Ethics Committee of Jinan University (Guangzhou, China).

**RNA isolation and RT-PCR.** Total RNA was extracted from 27 fresh fallopian tube tissues using an RNA isolation kit by Omega Bio-Tek Inc. (Norcross, GA, USA) according to the manufacturer's protocol. The mRNA concentration and purity were determined by 1.0% agarose gel electrophoresis, and the optical density (OD)<sub>260/280</sub> ratio was  $>1.8$ . Aliquots of mRNA (20  $\mu$ g) from each sample were reverse transcribed using oligo (dT)18 primer and the M-MLV reverse transcriptase (Promega Corp., Madison, WI, USA). The housekeeping gene glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) was used as an internal control to normalize the results for variations in the input cDNA amount or the RT efficiency. The forward primer for the amplification of the *VHL* gene (PCR product, 300 bp) was 5'-GTCTGAAGAGTACCGCCCTGAAG-3' and the reverse, 5'-GTGTCCCTGCATCTCTGAAGAG-3'. PCR amplification was carried out in the following conditions: initial denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 94°C for 15 sec, annealing at 60°C for 15 sec, and extension at 72°C for 1 min. The PCR products were verified by electrophoresis on a 1.5% agarose gel, and densitometry analysis was carried using the Bio-Rad Gel Doc 2000 Imaging system (Bio-Rad Laboratories, Hercules, CA, USA). Densitometrical values were used to calculate the relative expression ratio *VHL/GAPDH*.

**Western blotting.** The fresh fallopian tube tissues were homogenized and lysed on ice using cell lysis buffer (Beyotime Institute of Biotechnology, Shanghai, China) and a protease inhibitor cocktail. Following centrifugation at 10,000  $\times$  g for 15 min at 4°C, protein concentrations were determined using the Bicinchoninic Acid Protein Assay kit (Pierce Biotechnology, Inc., Rockford, IL, USA). Total proteins were denatured in Laemmli buffer (Bio-Rad Laboratories), fractionated using 10% one-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred onto nitrocellulose membranes. Blots were blocked for 2 h in TBST solution (20 mmol/l Tris pH 7.6, 137 mmol/l sodium chloride, 0.1% Tween-20) containing 10% non-fat dry milk, and incubated with primary antibodies targeting human pVHL (1:1,000; Cell Signaling Technology, Inc., Danvers, MA, USA) overnight at 4°C, or  $\beta$ -actin (1:3,000; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) for 1 h at room temperature with rocking. Subsequently, the blots were washed three times for 10 min each in TBST, followed by incubation for 1 h at room temperature with anti-rabbit and

anti-mouse horseradish peroxidase-linked species-specific immunoglobulin (IgG). The bound antibodies were detected with the enhanced chemiluminescence (ECL) system BeyoECL Plus (Beyotime Institute of Biotechnology). Band intensities were quantified by scanning densitometry, using the Bio-Rad Quantity One software (Bio-Rad Laboratories).

**IHC.** Paraffin-embedded sections of fallopian tissues at the proliferative (n=14) and secretory (n=13) phase were examined by IHC. Positive staining was evaluated with the standard streptavidin-biotin system (Mai-xin Bio, Fuzhou, China). The 4- $\mu$ m thick sections were deparaffinized in xylene, hydrated through graded alcohol, and incubated in antigen retrieval solution (0.01-mol/l sodium citrate buffer, pH 6.0) at 60°C for 16 min. Endogenous peroxidase activity was blocked by incubating the samples in 3% hydrogen peroxide for 10 min. Non-specific antibody binding was blocked by incubation with normal goat serum for 10 min. Mouse anti-human VHL monoclonal antibody (1:100; Mai-xin Bio) was used as the primary antibody, and the sections were incubated with the antibody overnight at 4°C. The secondary antibodies were biotinylated anti-mouse IgGs, and the reaction was developed with the streptavidin-peroxidase system. The diaminobenzidine Substrate-Chromogen system (Mai-xin Bio) was used as the color-developing substrate. The samples were observed under a fluorescence microscope (E400; Nikon, Tokyo, Japan).

**Statistical analysis.** Statistical analysis was performed with the SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). Data are expressed as mean  $\pm$  SD and were analyzed with one-way analysis of variance (ANOVA).  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**RT-PCR analysis.** *VHL* expression was analyzed in the human fallopian tube by RT-PCR. The *GAPDH* mRNA was first detected in twenty-seven fresh fallopian tube samples, and those that were positive were then used for detection of the *VHL* mRNA level (Fig. 1). The *VHL* mRNA levels in the human fallopian tubes are presented in Fig. 2. The *VHL* mRNA level in the fallopian tube was higher at the proliferative phase compared to the secretory phase of the menstrual cycle. There was no difference in the expression of *VHL* between the proliferative and the secretory phase ( $P > 0.05$ ).

**Western blotting.** The pVHL and  $\beta$ -actin protein expression levels were revealed by western blotting analysis in the fresh fallopian tube tissues. A single band for each protein was observed in all fresh fallopian tube tissues (Fig. 3A). The pVHL levels in the 27 fresh fallopian tube samples are shown in Fig. 3B. Although pVHL expression in fallopian tubes was increased at the proliferative phase compared to the secretory one, this difference was not statistically significant ( $P > 0.05$ ).

**IHC.** Positive staining corresponding to pVHL was detected by IHC in the cytoplasm of ciliated cells of the fallopian tube epithelium (Fig. 4). Positive staining for pVHL was detected in the 27 ciliated cells of the fallopian tube tissues.

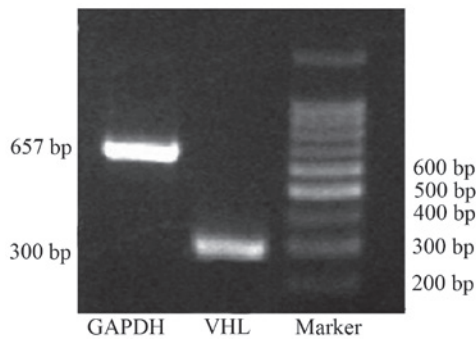


Figure 1. Gel image of polymerase chain reaction (PCR) products. Reverse transcription (RT)-PCR analysis of the 3-phosphate dehydrogenase (*GAPDH*) and von Hippel-Lindau (*VHL*) genes was performed in human fallopian tubes. Both genes are expressed in the human fallopian tube samples.

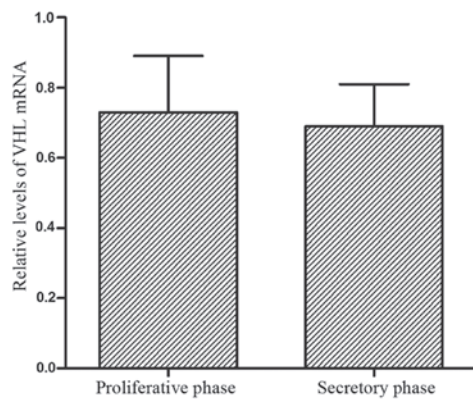


Figure 2. Von Hippel-Lindau (*VHL*) mRNA expression in human fallopian tubes at the proliferative and the secretory phase of the menstrual cycle were measured by reverse transcription polymerase chain reaction (RT-PCR). The 3-phosphate dehydrogenase (*GAPDH*) gene was used as an internal control. The *VHL* mRNA level in human fallopian tubes is higher at the proliferative compared to the secretory phase, but the difference is not significant ( $P>0.05$ ).

## Discussion

The *VHL* gene locates at the short arm of the human chromosome 3. It is ubiquitously expressed in a variety of organs, with particularly high levels of expression in the urogenital system, brain, kidney, sensory ganglia, and bronchial epithelium (11). pVHL, encoded by the *VHL* gene, is a multifunctional protein essential for endothelial extracellular matrix deposition, and inhibits cell motility (12). Moreover, pVHL can promote the assembly of actin and vinculin, and induce cell differentiation and growth arrest through integration of cell-cell and cell-extracellular matrix (ECM) signaling (13).

It was reported that pVHL is associated with embryogenesis and placenta development. The fallopian tube is the organ that provides the microenvironment for gamete transport, fertilization and preimplantation of the embryo. However, whether the *VHL* gene is expressed in human fallopian tubes has not been reported to date. pVHL can control ciliogenesis by stabilizing microtubule growth of the ciliated cells (14). In this study, pVHL-positive staining was detected in the cytoplasm of ciliated epithelial cells of human fallopian tubes. These results indicate that pVHL may be involved in the development of the

ciliated epithelial cells and the cell differentiation of cilia in the human fallopian tube.

The epithelium of human fallopian tube undergoes morphological and functional changes during the menstrual cycle. The number of tubal epithelial cells is low during the secretory phase of the menstrual cycle, and increase from the proliferative phase until the periovulatory period. At the periovulatory period, both secretory and ciliated cells are of equal size, with the secretory cells forming domes between the tufts of cilia (15). At approximately the time of ovulation, the secretory cells reach their peak activity, consequently reducing in height relative to the ciliated cells in tubal epithelium (16). The secretory cells can differentiate into ciliated cells, although this may be also considered as *prima facie* evidence for the existence of a multipotent precursor that can differentiate into other cell types via an intermediate cell type (17). A previous study indicated that pVHL can regulate the formation of primary cilia in the renal epithelium (18). Restoration of pVHL expression in *VHL*-negative human cancer cell lines was shown to enhance the frequency of ciliated cells, and knockdown of *VHL* in immortalized mouse kidney epithelial cells resulted in loss of primary cilia; these results suggest that *VHL* is necessary for the formation of the primary cilium (14,19). *VHL*-induced cell differentiation in renal epithelial cells was also reported (13). In this study, we demonstrated that the *VHL* gene is expressed in the human fallopian tube during the menstrual cycle, and that its expression at the proliferative phase is higher than the secretory phase, although the difference was not significant in our data. These results suggest that the *VHL* gene may regulate the differentiation of ciliated and secretory cells.

pVHL, as a tumor suppressor protein, regulates the proper extracellular fibronectin matrix assembly and the cell cycle. The fallopian tube epithelium can secrete fibronectin, and localizes at the luminal surface of the cells, especially on the tips of the cilia (20). Fibronectin is a regulator of various cellular activities, by promoting cell migration and spread, and extracellular matrix assembly. A previous study indicated that pVHL binds to fibronectin, and that *VHL* expression is associated with the deposition of assembled fibronectin (21). Overexpression of pVHL may increase fibronectin expression post-transcriptionally, as well as the secretion of extracellular fibronectin (22). Additionally, *VHL* gene mutations associated with disease result in fibronectin assembly defects, and pVHL-deficient cells fail to perform proper extracellular fibronectin matrix assembly (23). Therefore, pVHL physically interacts with fibronectin under physiological conditions, and this interaction can influence the ability of cells to assemble the extracellular fibronectin matrix. In the present study, the pVHL expression in the human fallopian tubes was not different between the proliferative and the secretory phase of the menstrual cycle. These results indicate that pVHL may not affect the fallopian tube during menstrual cycle through the interaction with fibronectin.

Integrins are  $\alpha\beta$  heterodimeric transmembrane proteins that provide a link between cells and the surrounding matrix through tightly regulated interactions with ligands. Integrins have also been used as molecular markers of endometrial receptivity. Sülz *et al* reported that a similar 'window of implantation' may exist in the fallopian tube, based on their observation of regulated expression of  $\beta 3$  integrin in



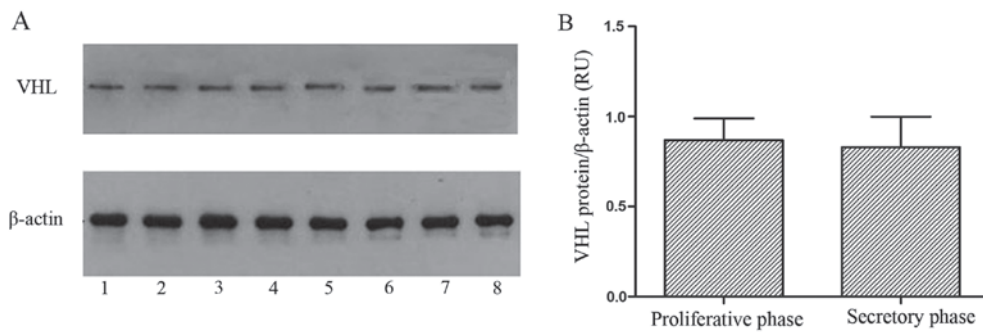


Figure 3. Western blotting was used to analyze the von Hippel-Lindau protein (pVHL) and  $\beta$ -actin expression in the human fallopian tubes. (A) The expression of pVHL is shown at the proliferative phase (lanes 1-4) and the secretory phase (lanes 5-8). (B) pVHL expression levels are elevated in human fallopian tubes at the proliferative phase compared to the secretory phase. There is no statistically significant difference between the proliferative and secretory phase expression levels ( $P>0.05$ ). RU, relative units.

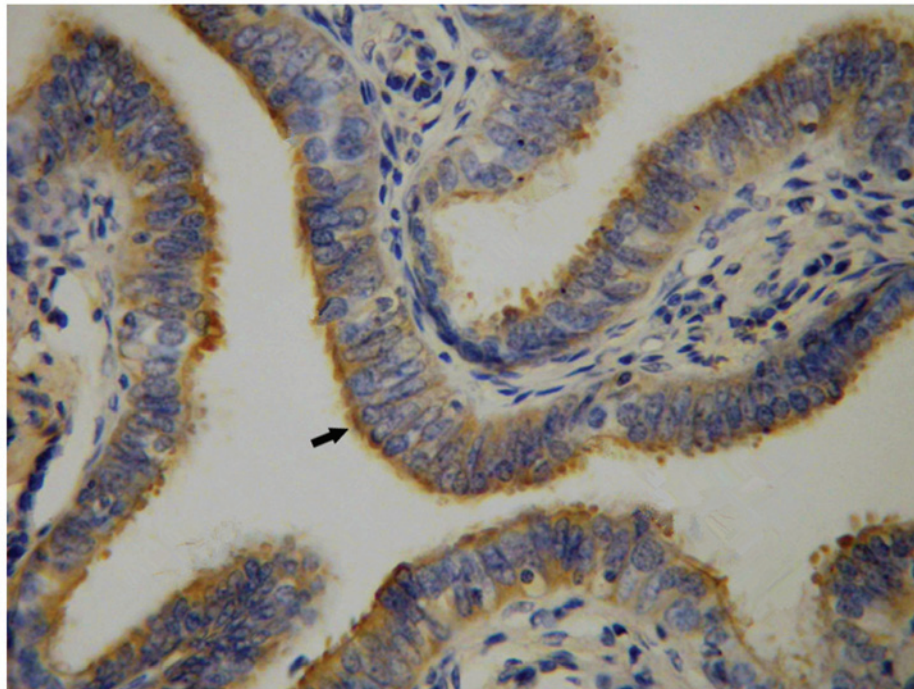


Figure 4. Immunohistochemistry was used to detect the Von Hippel-Lindau protein (pVHL) in the human fallopian tube epithelium. Positive staining corresponding to pVHL appears in the cytoplasm of the ciliated cells. The ciliated cells at the secretory phase are indicated by black arrows. Magnification, x200.

the human fallopian tube epithelium (24). A previous study demonstrated that VHL induces cell differentiation through cell-cell and ECM signaling (13). Cell-ECM signaling is mediated by integrins, and integrin signaling influences cell survival, proliferation and differentiation, which indicates that integrins may contribute to VHL-mediated cell differentiation (25). VHL-mediated tight junction and adherens junction assembly was associated to the downregulation of integrins (26). In addition, the presence of  $\beta$ 1-integrin fibrillar adhesions in VHL(+) cells at late confluence allowed the cells to firmly anchor to the substrate, and thus may be an important mechanism in controlling cell migration (27). In our study, the expression levels of VHL mRNA and protein in the fallopian tubes were not significantly different during the two stages of the menstrual cycle studied. This result indicates that VHL may regulate the differentiation of ciliated cells in the fallopian tube through integrin signaling.

The environment in the fallopian tube can affect the fertilization potential of the sperm and the embryo development. The transport of the spermatozoa and the pre-embryo is deemed to be aided by muscular contractions in the wall of the fallopian tube and the cilia in the tubal mucosa. Regulation of muscular activity and formation of cilia in the fallopian tube were shown to be affected by sex steroids, nitric oxides, and prostaglandins (PG) (28). PGE2 can increase HIF-1 $\alpha$  levels (29). Moreover, the HIF1- $\alpha$  subunit was identified and targeted for rapid proteasome-dependent degradation by the VHL E3 ubiquitin ligase complex at normal oxygen concentrations (30). Under normal conditions, the HIF1- $\alpha$  protein is rapidly degraded via the VHL-ubiquitin-proteasome pathway (31). Therefore, VHL gene expression in the fallopian tube may be associated with the function of the fallopian tube.

In conclusion, this study aimed to investigate VHL gene and protein expression in the human fallopian tube tissues

during the menstrual cycle. Expression levels of VHL mRNA and protein were not significantly different between the proliferative and the secretory phase. Our result may enhance the current understanding on the mechanism of fallopian tube associated-disease and functions. Additional studies are needed to investigate whether the VHL mRNA and protein expression levels can be the target of novel therapies against fallopian tube associated-disease.

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