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Mitochondrial tumor suppressor 1 is a target of AT-rich interactive domain 1A and progesterone receptor in the murine uterus

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Objective: Progesterone receptor (PGR) and AT-rich interactive domain 1A (ARID1A) have important roles in the establishment and maintenance of pregnancy in the uterus. In present studies, we examined the expression of mitochondrial tumor suppressor 1 (MTUS1) in the murine uterus during early pregnancy as well as in response to ovarian steroid hormone treatment.
Methods: We performed quantitative reverse transcription polymerase chain reaction and immunohistochemistry analysis to investigate the regulation of MTUS1 by ARID1A and determined expression patterns of MTUS1 in the uterus during early pregnancy.
Results: The expression of MTUS1 was detected on day 0.5 of gestation (GD 0.5) and then gradually increased until GD 3.5 in the luminal and glandular epithelium. However, the expression of MTUS1 was significantly reduced in the uterine epithelial cells of $Pgr^{cre/+}Arid1a^{f/f}$ and *Pgr* knockout (PRKO) mice at GD 3.5. Furthermore, MTUS1 expression was remarkably induced after P4 treatment in the luminal and glandular epithelium of the wild-type mice. However, the induction of MTUS1 expression was not detected in uteri of $Pgr^{cre/+}Arid1a^{f/f}$ or PRKO mice treated with P4.
Conclusion: These results suggest that MTUS1 is a novel target gene by ARID1A and PGR in the uterine epithelial cells.

Keywords: Mitochondrial Tumor Suppressor 1 (MTUS1); AT-rich Interactive Domain 1A (ARID1A); Uterus; Progesterone Receptor; Estrogen

INTRODUCTION

The endometrium is the tissue lining the inner cavity of the uterus and is a target tissue of ovarian steroid hormone. Estradiol (E2) stimulates endometrial proliferation and growth, while progesterone (P4) suppresses E2 induced epithelial cell proliferation, concomitant with initiation of stromal cell differentiation. These dynamic changes are necessary for embryo implantation and successful pregnancy [1]. The endometrium undergoes well-defined and regulated gene expression in preparation for implantation [2].

The physiological effects of P4 are mediated by the progesterone receptor (PGR). P4 and its receptor (PGR) play a central role in reproductive events associated with the establishment and maintenance of pregnancy. PGR regulates implantation, decidualization, and glandular development via a complex paracrine signaling network [3-5]. Dysregulation of PGR and its signaling at the time of implantation is a sign of P4 resistance [6]. P4 resistance is associated with pregnancy loss, and infertility due to endometriosis [2,7]. Endometriosis is a representative disease of P4 resistance. The eutopic endometrium in women with endometriosis expresses aberrant gene activation in response to the ovarian steroid hormones. Disturbance of P4 signaling in the endometrium results in the impaired decidualization and establishment of ectopic endometrial implants. Genes involved in cell cycle control are

up-regulated in endometrium from endometriosis, while a negative regulator of growth factor signaling, such as mitogen-induced gene 6, is significantly decreased [8].

AT-rich interactive domain 1A (ARID1A) is a tumor suppressor gene in a variety of human cancers. ARID1A is frequently mutated in endometrium-related neoplasms including ovarian clear cell carcinoma, ovarian endometrioid carcinomas, and uterine endometrioid carcinomas, all of which arise from endometrial epithelium [9,10]. Furthermore, ARID1A protein levels are significantly lower in the eutopic endometrium of women with endometriosis [11]. ARID1A plays a critical role with PGR in modulating epithelial proliferation of the mouse uterus which is a critical requisite for fertility [11]. However, an understanding of the pathophysiological effects of ARID1A loss remains poor and the function of ARID1A in the female reproductive tract has remained elusive.

Mitochondrial tumor suppressor 1 (*MTUS1*) gene is known as a candidate tumor suppressor gene encoding a family of angiotensin II receptor-interacting proteins (ATIP) [12]. It is located at chromosome 8p21.3-22 in humans [13], and its allelic losses have been documented to be associated with many cancer types such as colon, pancreas, breast, lung, bladder, and prostate cancers. *MTUS1* produces six different transcript variants by alternative splicing. Among those, five transcripts lead to five protein isoforms such as ATIP1, ATIP2, ATIP3a, ATIP3b, and ATIP4 [14]. ATIP2 and ATPI3a variants are noted to be only specific to human [15], the restoration of ATIP1 protein inhibited cell proliferation in tongue squamous cell carcinoma cell lines [16]. ATIP1 is known as a mitochondrial protein and is involved in the AT II-mediated apoptotic cell death [17]. In addition, ATIP3 was associated with microtubules and resulted in the delay of mitosis and limitation of cell migration [18]. MTUS1/ATIP3a down-regulation is demonstrated in human salivary adenoid cystic carcinoma, and it plays an important role in cell proliferation, migration and invasion [19]. Although the effect of *MTUS1* has been elucidated in the cell proliferation of several carcinomas, the expression of MTUS1 in female reproductive tissue has remained elusive. Furthermore, there is no information that MTUS1 is expressed or functioning in the uterus.

In order to explore the regulation of MTUS1 expression in the uterus, we investigated the spatiotemporal expression of MTUS1 in endometrium during early pregnancy. We also evaluated the regulation of MTUS1 in response to ovarian steroid hormones in the uterus.

MATERIALS AND METHODS

Animals and tissue collection

All mouse experiments were approved by the Institutional Animal Care and Use Committee of Michigan State University. For the uteri samples during early pregnancy, wild C57BL/6 female mice at 8 weeks age were individually mated with wild-type male mice and uteri were collected at different time points of pregnancy. The initiation of pregnancy was marked by the presence of the postcoital vaginal plug as day 0.5 of gestation (GD 0.5) for early pregnancy study. In order to investigate the expression of MTUS1 by PGR and ARID1A in the uterus, we used *Pgr* knockout (PRKO) and $Pgr^{cre/+}Arid1a^{f/f}$ ($Arid1a^{d/d}$) mice [11,20]. PRKO mice have a germline loss of function mutation at the *Pgr* locus and do not express either A or B isoforms of *Pgr* [20]. We previously generated mice with conditional ablation of *Arid1a* in the PGR positive cells ($Arid1a^{d/d}$) to study the role of *Arid1a* in the uterus [11]. Uterine tissues were collected from both horns then were stored at –80°C for RNA or fixed in 4% paraformaldehyde (vol/vol) and paraffin embedded.

To study MTUS1 expression by steroid hormone regulation, wild-type C57BL/6 mice, $Arid1a^{d/d}$ or PRKO mice at 6 weeks age underwent bilateral ovariectomy. After at least 2 weeks to eliminate endogenous ovarian hormone completely, the mice were given subcutaneous injection with one of the following regimen: vehicle (sesame oil), P4 (1 mg/mouse), E2 (0.1 μg/mouse) or E2+P4 (E 0.1 μg/mouse followed by P4 1 mg/mouse) (n = 3 per genotype per treatment per time point). The injections were subsequently repeated every 24 hours for the 3 day treatment. The uteri were collected at 6 hours or 3 days after steroid hormone injection.

RNA isolation and real-time quantitative polymerase chain reaction

Total RNA was isolated from uteri using Qiagen RNeasy total RNA isolation kit (Qiagen, Valencia, CA, USA). The expression levels of *MTUS1* were quantified by real-time quantitative polymerase chain reaction (RT-qPCR) using an Applied Biosystems StepOnePlus system according to the manufacturer's instructions (Applied Biosystem, Foster City, CA, USA). The cDNAs were synthesized with MMLV Reverse Transcriptase (Invitrogen Corp., Carlsbad, CA, USA) by the use of 1 μg of total RNA primed with random hexamer primers according to the manufacturer's instructions. RT-qPCR was performed on cDNA to assess the expression levels of genes of interest with primers, by using SYGR green and 96-well optical plates, with an Applied Biosystems StepOnePlus (Applied Biosystem, USA). *Mtus1* and 18S were detected with the following primer pairs: *Mtus1* F (5'- ACAGAAGATGGATCGCGTTATG-3') and *Mtus1* R (5'- CCCCGTGACTCACTGAAGG-3'), and 18SF (5'- GTAACCCGTTGAACCCCATT-3') and 18SR (5'-CCATCCAATCGGTAGTAGCG-3'). Experimental *Mtus1* data were normalized to 18S ribosomal RNA. Analysis of Mtus1 mRNA expression was first undertaken by the standard curve method, and results were corroborated by cycle threshold (CT) values assessing levels of gene expression. All data are presented as mean±standard error of the mean. A

p-value of less than 0.05 ($p<0.05$) was considered statistically significant. All statistical analysis was performed by Instat package from GraphPad (San Diego, La Jolla, CA, USA).

Immunohistochemistry

Uterine sections of 6 μm thickness were blocked with 10% normal goat serum in phosphate-buffered saline (PBS) (pH 7.5) for immunohistochemistry. Sections were exposed to appropriate primary antibody anti-MTUS1 (ab198176, Abcam, Cambridge, UK) in 10% normal goat serum in PBS (pH 7.5) overnight at 4°C. Sections were incubated with the appropriate secondary antibody (Vector Laboratories, Burlingame, CA, USA). This anti-MTUS1 antibody expects to detect endogenous levels of total MTUS1 protein because the immunogen is full length protein corresponding to human MTUS1. Sections were incubated with biotinylated goat anti-rabbit 2nd antibody (BA-1000; Vector Laboratories, USA). Following exposure to the horseradish peroxidase-conjugated streptavidin substrate, positive immunoreactivity (brown precipitate) was detected using the Vectastain Elite DAB kit (Vector Laboratories, USA) and hematoxylin (Biocare Medical, Pacheco, CA, USA) was used for a nuclear counterstain.

RESULTS

The expression of MTUS1 in the uterus during early pregnancy

To investigate the expression pattern of MTUS1 in mouse uteri during early pregnancy, we performed immunohistochemistry from GD 0.5 to GD 7.5 uteri of natural pregnancy (Figure 1). The initiation of pregnancy was marked by the presence of the postcoital vaginal plug (GD 0.5). The expression of MTUS1 proteins were weakly detected in the luminal epithelium (LE), glandular epithelium, and stroma but not myometrium at GD 0.5. Interestingly, MTUS1 proteins were strongly expressed in the luminal and glandular epithelium of GD 2.5 and GD 3.5. However, the weak expression of MTUS1 in stroma was not changed. After embryo implantation, the expression of MTUS1 was not observed in uterus including within the primary decidual zone at GD 4.5. Furthermore, we could not observed MTUS1 proteins in the secondary decidual zone or in embryos. Immunohistochemistry with normal rabbit immunoglobulin G was performed as a negative control. Our immunohistochemistry results suggest that MTUS1 may play an important role for preparing endometrial receptivity in uterine epithelial cells at the pre-implantation stage.

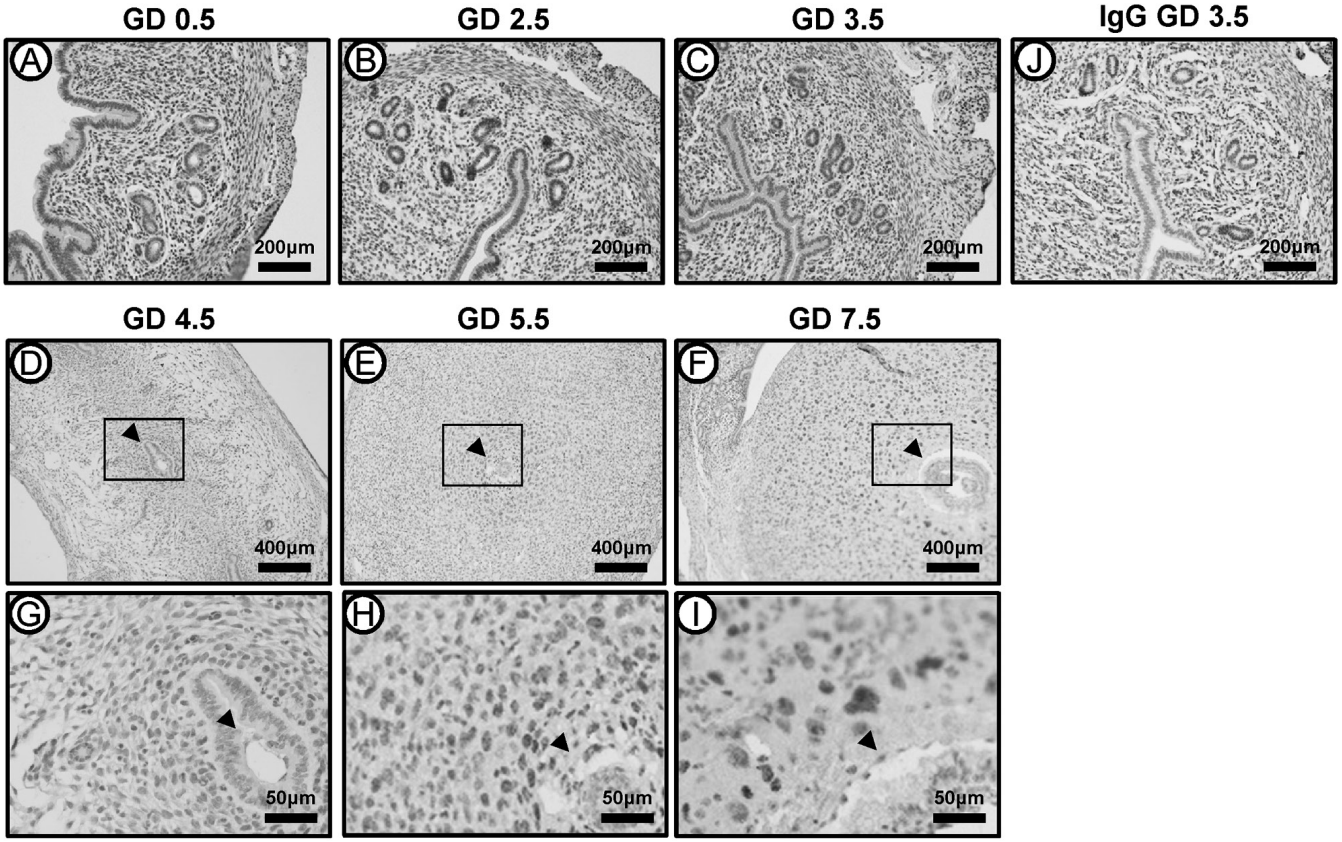

Figure 1. The expression pattern of mitochondrial tumor suppressor 1 (MTUS1) during early pregnancy. The localization of MTUS1 proteins was investigated by immunohistochemistry in uteri of mice on GD 0.5 (A), GD 2.5 (B), GD 3.5 (C), GD 4.5 (D and G), GD 5.5 (E and H), and GD 7.5 (F and I) (n = 3 per timepoint). Normal Rabbit immunoglobulin G was used as a negative control (J). GD, day of gestation. Arrow indicates embryo.

Regulation of MTUS1 expression by ARID1A and PGR at pre-implantation stage

PGR and ARID1A have a critical role in modulating epithelial proliferation at the pre-implantation stage which is a critical requisite for uterine receptivity [11]. To determine whether the expression of MTUS1 is regulated by PGR and ARID1A in the mouse uterus, uteri were collected from wild type, *Arid1a*$^{d/d}$, and PRKO mice at GD 3.5 and the expression of *Mtus1* was examined by real-time qPCR. As shown in Figure 2A, the level of *Mtus1* mRNA was significantly decreased in PRKO and *Arid1a*$^{d/d}$ mice compared to wild type mice.

Next, we performed immunohistochemistry to determine the spatial expression of MTUS1 in the uteri from wild type, *Arid1a*$^{d/d}$, and PRKO mice at GD 3.5 [11,21]. MTUS1 signaling was seen in luminal and glandular epithelium of wild type mice. However, the expression of MTUS1 was not detected in uterine epithelial cells of *Arid1a*$^{d/d}$ and PRKO mice. These data suggest that MTUS1 is a target of ARID1A and PGR in the uterus at GD 3.5.

Regulation of MTUS1 expression by ovarian steroid hormone in murine uterus

During early pregnancy, P4 and temporal E2 induction are important for preparing blastocyst implantation [4,5]. To determine whether there is a steroid hormone effect on MTUS1 expression, we examined the MTUS1 expression in uteri of ovariectomized mice which were treated by different steroid hormone regimen; vehicle (sesame oil), P4 (1 mg/mouse), E2 (0.1 μg/mouse), or E2+P4 (Figure 3). The basal level of MTUS1 proteins was weakly detected in luminal and glandular epithelium of the ovariectomized mice treated with vehicle. The expression of MTUS1 protein was induced in luminal and glandular epithelium after 6 hours of P4 treatment. The induction of MTUS1 proteins was remarkably increased in epithelial cells as well as stromal cells after 3 days of P4 treatment compared to 6 hours. E2 treatment also increased the expression of MTUS1 in uterine epithelial cells but the induction was weaker than P4 treatment. Furthermore, E2+P4 treatment revealed a strong induction of MTUS1 in the uterine epithelium as well as stroma. These results suggest that P4 and E2 regulate MTUS1 expression in the uterus.

P4 dependent regulation of MTUS1 expression by ARID1A and PGR

MTUS1 expression was decreased in *Arid1a*$^{d/d}$ and PRKO mice uterus during early pregnancy. P4 and PGR signaling has a critical role for implantation, decidualization and successful pregnancy. To investigate whether the P4 regulation on MTUS1 is relevant to PGR or ARID1A, ovariectomized wild-type, *Arid1a*$^{d/d}$, or PRKO mice were treated with vehicle (sesame oil) or P4 for 6 hours. Then the levels of MTUS1 protein were examined using immunohistochemistry (Figure 4). As we observed in Figure 3, P4 treatment considerably increased the expression of MTUS1 protein in luminal and glandular epithelium compared to vehicle treated control. However, there was no signal of MTUS1 expression in the uteri of PRKO or *Arid1a*$^{d/d}$ mice. These results indicate that PGR and ARID1A are essential for MTUS1 regulation in luminal and glandular epithelium by P4.

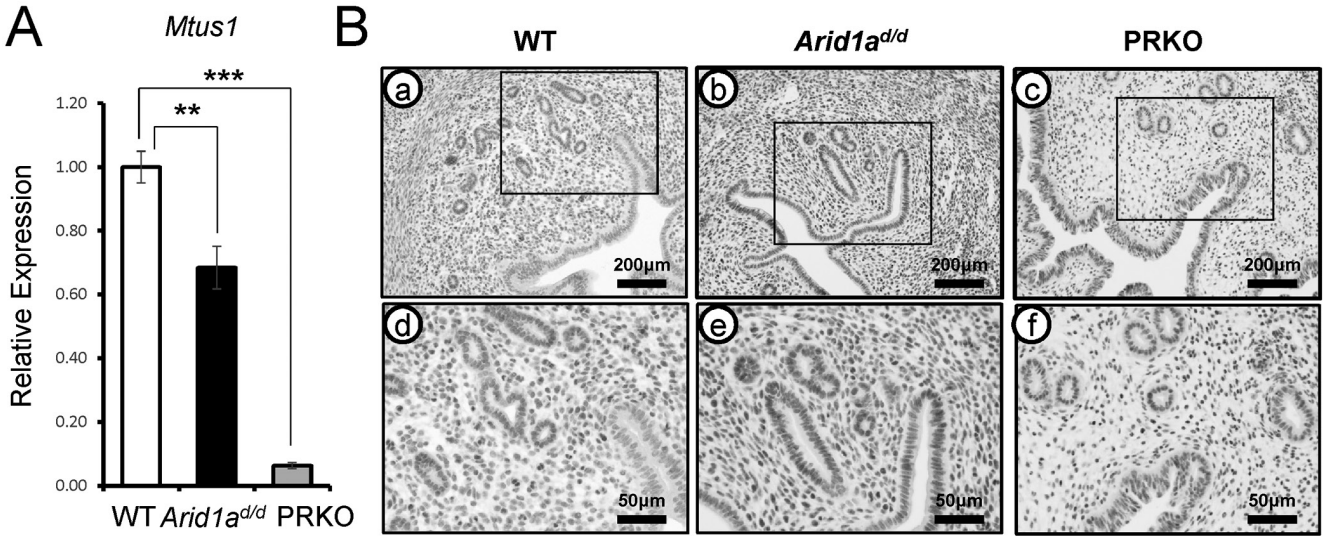

Figure 2. Regulation of mitochondrial tumor suppressor 1 (MTUS1) expression in the uteri of wild-type, *Arid1a*$^{d/d}$, and PRKO mice. (A) The expression of *Mtus1* from wild-type control, *Arid1a*$^{d/d}$, and used *Pgr* knockout (PRKO) mice uteri by quantitative reverse transcription polymerase chain reaction (RT-qPCR). Total RNA used for the real-time qPCR assay was prepared from control and *Arid1a*$^{d/d}$ mice uteri at day 3.5 of gestation (GD 3.5). The results represent the mean±standard error of the mean of three independent RNA sets, $p<0.05$. (B) The localization pattern of MTUS1 proteins by immunohistochemistry in the uteri of wild-type (a and d), *Arid1a*$^{d/d}$ (b and e), and PRKO (c and f) mice. Uterine sections were collected from wild-type, *Arid1a*$^{d/d}$, and PRKO mice at GD 3.5 (n = 5 per genotype).

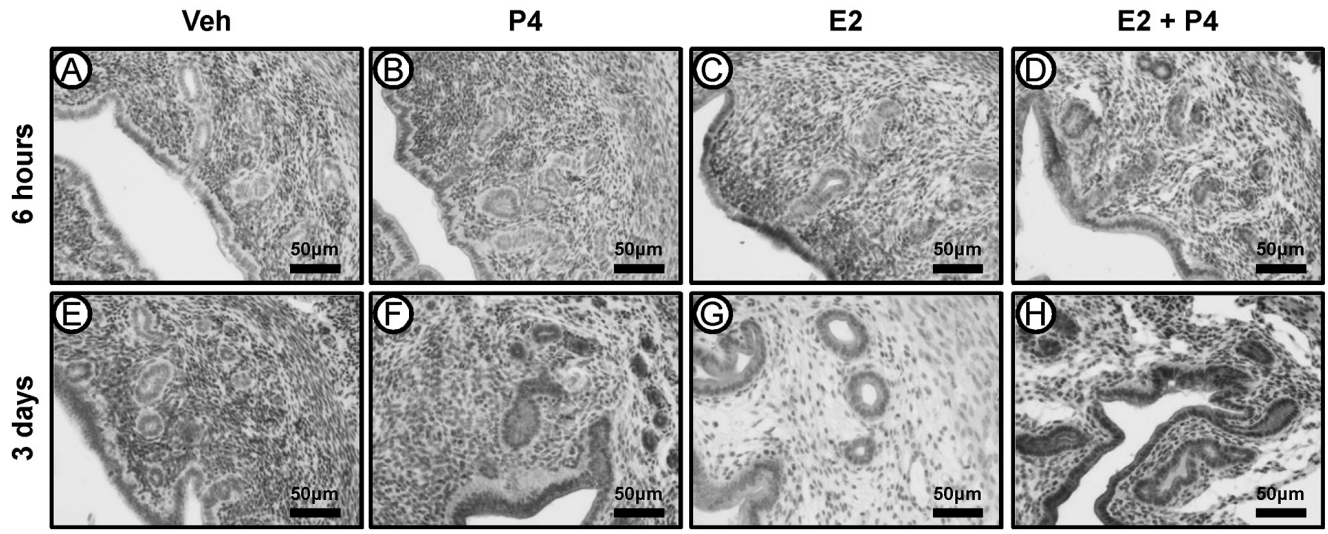

Figure 3. Regulation of mitochondrial tumor suppressor 1 (MTUS1) expression by progesterone (P4) and estradiol (E2). The spatial expression pattern of MTUS1 was examined by immunohistochemistry in the uteri from wild type mice treated with vehicle (A and E), P4 (B and F), E2 (C and G), or E2+P4 (D and H) for 6 hours (A-D) or 3 days (E-H) (n = 5 per treatment per timepoint).

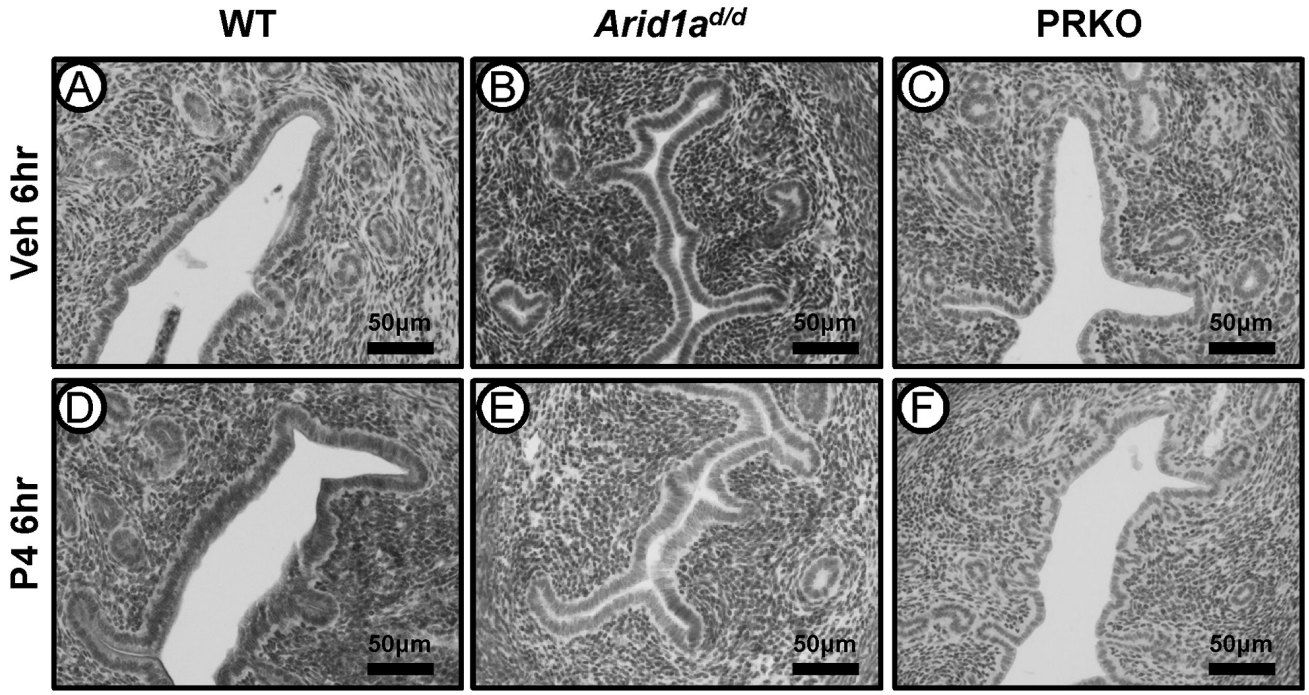

Figure 4. The P4 dependent regulation of mitochondrial tumor suppressor 1 (MTUS1) expression by AT-rich interactive domain 1A (ARID1A) and progesterone receptor (PGR). Immunohistochemical analysis of MTUS1 proteins in the vehicle (A-C) or P4 (D-F)-treated uteri from wild type (A and D), *Arid1a*$^{d/d}$ (B and E), and *Pgr* knockout (PRKO) (C and F) (n = 5 per genotype per treatment).

DISCUSSION

This study demonstrates that *MTUS1* is a P4-PGR signaling target gene in the murine uterus. The ovarian steroid hormones tightly regulate the uterine endometrium, and stimulate uterine cell proliferation by various mechanisms, such as induction of growth factors, paracrine signaling, and by direct regulation of cell cycle genes [22]. A transgenic mouse with a null mutation in the *Pgr* gene (PRKO) is a well-designed experimental model to understand the essential role for PGR in P4-mediated uterine responses [20]. P4 induces the expression of MTUS1 protein in uterine epithelial cells of wild type mice but not PRKO mice at GD 3.5. Increased P4 rapidly suppressed endometrial proliferation by downregulation of

genes related with DNA replication such as proliferating cell nuclear antigen, cellular marker of proliferation, thymidine kinase 1, forkhead box protein O1 [23]. PGR is upregulated in the LE from GD 0.5 to GD 3.5 and in both epithelial and stromal cells and then abruptly decreased in luminal epithelial cell at GD 4.5 [24]. This dynamic means of regulation of PGR is evidence of its critical role in a successful pregnancy.

The proliferative switch from uterine epithelial cell to stroma normally occurs at GD 3.5 in mice. This suggests that P4-dependent proliferation in the stromal cell is regulated by stromal *Pgr* not epithelial *Pgr*. Stromal cell proliferation and differentiations are prerequisites to a receptive uterus for embryo implantation. However, tissue-specific knockout of *Pgr* in the uterine epithelial cells of mice resulted in aberrant proliferation of epithelial cells in the absence of P4 action [25]. Our results showed that the MTUS1 expression was markedly enhanced in uterine epithelial cells of wild-type mice at GD 3.5. This suggests that MTUS1 might have an important role in regulation of epithelial proliferation.

MTUS1 is a tumor suppressor gene encoding a family of ATIPs. The ATIP proteins exhibit distinguishing motifs in the amino-terminal end, indicating that they have distinct cellular activities [14]. MTUS1 downregulation has been found in various epithelial cancers. The levels of MTUS1 expression were significantly reduced in breast cancer [26]. Decreased expression of MTUS1/ATIP is related with upregulated proliferation, poor differentiation, and poor prognosis in squamous cell carcinoma of the tongue [16]. ATIP3a is involved extracellular signal-regulated kinase (ERK) and epithelial-to-mesenchymal transition (EMT). Reconstitution of ATIP3 inhibits tumor growth, which led to an increase in survival rate in ovarian carcinoma via down-regulation of the ERK/EMT pathway [27]. When MTUS1/ATIP3 expression was restored, ATIP3 changed the velocity of cell division by prolonged metaphase, thereby leading to a reduced number of proliferative cells [28]. Our previous study showed that mice with conditional ablation of *Arid1a* in *Pgr* positive cells were sterile due to defects of implantation and decidualization [11]. ARID1A directly interacts with PGR to repress the genes related to cell cycle and DNA replication at the pre-implantation stage [11]. *Arid1a* has been known as a tumor suppressor gene, and is the most common mutated gene among gene encoding subunits of SWitch/Sucrore NonFermentable (SWI/SNF) complex [29]. Down-regulation of MTUS1 expression in *Arid1a*$^{d/d}$ mice suggests that MTUS1 may play a role as a mediator of tumor suppressor ARID1A in the uterus.

Endometriosis is an E2-dependent disease affecting fertility. P4 resistance is a well-established phenomenon seen in endometriosis and the eutopic endometrium [2,6]. P4 resistance is a hallmark of implantation failure and is associated with measurable changes in endometrial gene expression [30,31]. The eutopic endometrium in women with endometriosis exhibits aberrant gene expression in response to P4 and E2. MTUS1 proteins were not detected in uteri of *Arid1a*$^{d/d}$ and PRKO mice treated with either vehicle or P4. ARID1A proteins are strongly expressed in the stromal and epithelial cells of endometrium from the proliferative phase and early, mid, and late secretory phases in women [11]. ARID1A proteins are also consistently strong in the nucleus of epithelial and stromal cells of mouse uterus during early pregnancy [11]. PGR and ARID1A were dysregulated in the eutopic endometrium of women with endometriosis [11,31]. In our previous study, we found ARID1A protein directly interacts with PR-A in Ishikawa cells [11]. The expression pattern of MTUS1 is matched with PGR expression until embryo implantation. However, MTUS1 protein is not detected in decidual cells [11]. Therefore, our results suggest that the fine regulation of MTUS1 is important to prepare receptive endometrium.

MTUS1 is a tumor suppressor gene that is reported to be frequently down-regulated in a variety of human cancers including pancreas, colon, bladder, ovarian, breast cancers, gastric, lung cancers [12]. It is also implicated in several types of pathologies such as cardiac hypertrophy, atherosclerosis, and SLE-like lymphoproliferative diseases [12]. However, there is no literature that investigates the function of MTUS1 in the uterus. Overall, these findings show for the first time that the expression of MTUS1 is tightly regulated through PGR and ARID1A in the uterine epithelium during early pregnancy. Our findings will provide further insight into PGR and ARID1A signaling mechanisms in the uterus.

CONFLICT OF INTEREST

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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