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TEMPORAL REGULATION OF *PATL2* TRANSCRIPT LEVELS DURING OOCYTE MATURATION AND EMBRYO DEVELOPMENT: AN *IN SILICO* ANALYSIS

OOSİT OLGUNLAŞMASI VE EMBRİYO GELİŞİMİ SIRASINDA PATL2 TRANSKRİPT DÜZEYLERİNİN ZAMANSAL DÜZENLENMESİ: BİR SİLİCO ANALİZİ

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ABSTRACT

Objective: Female infertility is a relatively frequent disorder of the reproductive system, and its molecular etiology and associated cellular mechanisms remain unexplained. Certain mutations in *PATL2* gene have been identified to cause female infertility, characterized by oocyte maturation arrest and oocyte meiotic deficiency. *PATL2* encodes an RNA-binding protein functioning as a translational repressor in oocyte maturation; therefore, proper temporal control of *PATL2* expression was suggested to be essential for normal oocyte maturation.

Methods: Transcriptomics data was used to analyze temporal regulation of PATL2 transcript levels during oocyte maturation and embryo development in mice, using R programming language.

Results: Based on in silico analysis, mRNA expression of the PATL2 gene in mouse oocytes was found to increase from the primordial follicle stage to the primary follicle stage ($p \leq 0.05$). Its expression was reported to stay high in the primary and secondary follicle stages, then to decrease in the antral follicle stages (tertiary follicle stages). Besides, *PATL2* expression was shown to be lower in metaphase 2 (MII)-stage oocytes compared to germinal vesicle (GV)-stage oocytes in mice ($p \leq 0.05$). Moreover, it was observed that *PATL2* transcript levels even change during embryo development.

Conclusion: Data in the present study points to the temporal regulation of PATL2 expression at the transcription level during oocyte growth, supporting previous research performed at the protein level. Considering the importance of PATL2 in oocyte maturation arrest and female sterility, and also the number of PATL2 pathogenic variants previously identified, a better mechanistic understanding of PATL2 regulation at the transcriptional level in oocytes might have clinical significance and guide the development of novel treatment strategies.

Keywords: *PATL2* gene, oocyte maturation arrest, oocyte growth, germinal vesicle arrest, secondary follicle stage, female fertility, gene regulation

ÖZ

Amaç: Kadın kısırlığı üreme sisteminin nispeten sık görülen bir bozukluğudur ve moleküler etiyolojisi ve ilişkili hücresel mekanizmaları henüz açıklanamamıştır. *PATL2*'deki belirli mutasyonların, oosit olgunlaşmasının durması ve oosit meiotik eksikliği ile karakterize edilen kadın kısırlığına yol açtığı belirlenmiştir. *PATL2*, oosit olgunlaşmasında translasyonel baskılayıcı olarak işlev gören bir RNA bağlayıcı protein kodlar; bu nedenle, *PATL2* ekspresyonunun uygun zamansal kontrolünün normal oosit olgunlaşması için elzem olduğu ileri sürülmüştür.

Yöntem: Bu çalışmada, R programlama dilini kullanarak, farelerde oosit olgunlaşması ve embriyo gelişimi sırasında *PATL2* transkript seviyelerinin zamansal düzenlenmesini analiz etmek için transkriptomik verileri kullanılmıştır.

Bulgular: Fare oositlerinde *PATL2* geninin mRNA ekspresyonunun primordial folikül aşamasından birincil folikül aşamasına kadar arttığı ve ekspresyonunun birincil ve ikincil folikül aşamalarında yüksek kaldığı, ardından antral folikül aşamalarında (üçüncül folikül aşaması) azaldığı gösterilmiştir. Ayrıca, farelerde *PATL2* ekspresyonunun metafaz 2 (MII) aşamasındaki oositlerde germinal vezikül (GV) aşamasındaki oositlere kıyasla daha düşük olduğu ve *PATL2* transkript seviyelerinin embriyo gelişimi sırasında bile değiştiği bulunmuştur.

Sonuç: Mevcut çalışmadaki veriler, oosit büyümesi sırasında *PATL2* ekspresyonunun transkripsiyon seviyesinde zamansal olarak düzenlendiğini ve protein seviyesinde gerçekleştirilen önceki araştırmaları desteklediğini göstermektedir. *PATL2*'nin oosit matürasyon durması ve dişi kısırlığındaki önemi ve tanımlanan *PATL2* patojenik varyantlarının sayısı göz önüne alındığında, oositlerde transkripsiyonel seviyede *PATL2* regülasyonunun daha iyi bir mekanistik anlayışı klinik öneme sahip olabilir ve yeni tedavi stratejilerinin geliştirilmesine rehberlik edebilir.

Anahtar Kelimeler: *PATL2* geni, oosit olgunlaşmasının durması, oosit büyümesi, germinal vezikül durması, sekonder folikül evresi, kadın doğurganlığı, gen regülasyonu

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Introduction

Human oocyte maturation includes nuclear and cytoplasmic maturation, and abnormalities in these processes lead to female infertility and recurrent failure of in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) attempts. Certain mutations in *PATL2* (PAT1 homolog 2) gene have been identified to result in female infertility in humans, characterized by oocyte maturation arrest and oocyte meiotic deficiency in last years.[1-25] Most of the oocytes with *PATL2* mutations are arrested at the germinal vesicle (GV) stage.[22] Oocytes and zygotes from *PATL2* knockout mice exhibit morphological and developmental defects.[3] The absence of *PATL2* results in the deregulation of expression levels of a select number of highly relevant genes involved in oocyte maturation and early embryonic development.[3] PATL2 regulates the maternal transcriptome in immature oocytes.[21] The GV oocytes from PATL2$^{-/-}$ mice exhibit lower maternal mRNA expression and decreased levels of protein synthesis.[21] The protein levels of PATL2 in oocytes were reported to increase or decrease depending on the particular mutation.1-25 For instance, the *PATL2*^{Y217N} mutation leads to decreased levels of PATL2 ubiquitination and degradation in oocytes, resulting in abnormal protein levels of PATL2.[8] Reduced PATL2 levels have also been shown to result in the increased apoptosis levels of ovarian granulosa cells (GCs).[10]

Recently, Ye et al. identified novel *PATL2* variants in which amino acids altered are highly conserved in mammals, suggesting that these *PATL2* mutations impair the physiological function of the protein.[24] Although several studies reported the changes in PATL2 protein levels during oocyte maturation and embryo development in mice by performing immunostaining and immunoblotting, data regarding *PATL2* expression at the mRNA level in the course of oocyte maturation and embryo development are still lacking. This is of high importance in order to determine if *PATL2* expression is regulated mainly at the transcriptional level or post-transcriptionally. Here, changes in *PATL2* transcript levels were studied in silico during mouse oocyte growth and embryo development, providing novel insights into the regulation of *PATL2* gene expression in oocytes. It was found that *PATL2* mRNA levels peak in oocytes from primary and secondary follicle stages, then start to decrease gradually towards the large antral follicle stage. Similarly, GV oocytes have higher *PATL2* transcript levels compared to MII (metaphase 2) oocytes. In terms of embryo development in mice, *PATL2* mRNA levels decrease from 1-cell embryo to 8-cell embryo and then increase at the blastocyst stage, pointing to a dynamic regulation of *PATL2* gene expression. Lastly, it was found that the depletion of CTCF (both a classical repressor and activator of transcription in oocytes) leads to increased mRNA expression of *PATL2* in mouse oocytes. Combined, data in the present study suggest that *PATL2* expression is highly regulated at the mRNA level, supporting data from previous research performed at the protein level. Considering the importance of PATL2 in oocyte maturation arrest and female infertility, a better understanding of *PATL2* regulation at the transcriptional level in oocytes might be of high clinical significance.

Methods

Datasets

In the present study, the following transcriptomics datasets were used: GSE335129, GSE1166730, GSE174529 and GSE11664.26 The model organism used in the construction of these datasets is the mouse (*Mus musculus*). Gene expression datasets with a minimum sample size (n) of 10 were selected to be analyzed in this study. More experimental detail (such as overall experimental design, platforms used, etc.) about these publicly available datasets can be found at Gene Expression Omnibus (GEO) (Table 1).[31, 32] Each sample was shown as a different data point in the plots. Datasets used were also indicated in figure captions (located at the bottom right of the plots). Gene expression values shown and analysed in each plot were obtained from a unique dataset, without any meta-analysis performed.

Informed consent and institutional review board approval are not applicable for the current study.

Table 1. Details of the datasets used in the present study.

Dataset	Sample size (n)	Method	Tissue/Cell type
GSE3351	20	Expression profiling by array	Oocytes collected from ovary by follicle stage
GSE11667	16	Expression profiling by array	Fully-grown germinal vesicle (GV) oocytes from young (6 weeks old) or old (66 weeks old) mice
GSE1745	20	Expression profiling by array	Preimplantation embryos
GSE11664	10	Expression profiling by array	CTCF-depleted mouse oocytes

Data Analysis and Visualization

Data analysis and visualization in this study were performed using the R statistical programming language (version '3.15')[33], using the following R packages: readxl34, tidyverse[35], ggpubr[36], knitr[37], and rmarkdown[38], as previously reported.[39, 40] The Shapiro-Wilk normality test was used to test the normality of the expression data. When *p*-value is bigger than 0.05, normal distribution of the data could be assumed, and therefore, a t-test was performed; otherwise, a Wilcox test was used to compare group means.[36, 41] Mean expression values were shown in red on boxplots / violinplots. R scripts (R markdown files) used in the data analysis are available as supplementary files to make this study completely reproducible. In data visualization, geom_boxplot() and geom_violin() functions from ggplot

R package (one of tidyverse packages) was particularly used.[35] Statistical analyses shown on the plots was performed using ggpubr package.[36] In the comparison of group means, $p < 0.05$ significance cut off was used. ns (non-significant): $p > 0.05$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$.

Results

Changes in *PATL2* expression during mouse oocyte growth from primordial follicle stage to large antral follicle stage

In the first part of the analysis, changes in *PATL2* expression were studied at the mRNA level in mouse oocytes by follicle stage during oocyte development using GSE3351 dataset, and found that mRNA expression of *PATL2* gene in mouse oocytes increases from the primordial follicle stage to the primary follicle stage (Figure 1). Its expression stays high in the primary and secondary follicle stages, then decreases in the antral follicle stages (tertiary follicle stages) (Figure 1). *PATL2* expression is even lower in the large antral follicle stage compared to the previous small antral follicle stage (Figure 1). Yet, its expression is still high in the large antral follicles compared to that in the primordial follicles (Figure 1).

Differential expression of *PATL2* between germinal vesicle (GV)- and metaphase 2 (MII)-stage oocytes.

Subsequently, it was found that *PATL2* expression is lower in metaphase 2 (MII)-stage oocytes compared to germinal vesicle (GV)-stage oocytes in mice, performing in silico data analysis using data from GSE11667 (Figure 2). This is true for oocytes from both young (6 weeks old) and old (66 weeks old) mice (Figure 2). Others showed that PATL2 protein levels are lower in MI and MII oocytes compared to GV oocytes. Combined, this data suggests that *PATL2* expression in oocytes might be regulated at the transcriptional level, rather than at the translational level over the course of oocyte maturation, since PATL2 protein levels parallel *PATL2* mRNA levels in oocytes during the process of their maturation from GV to MII stage.

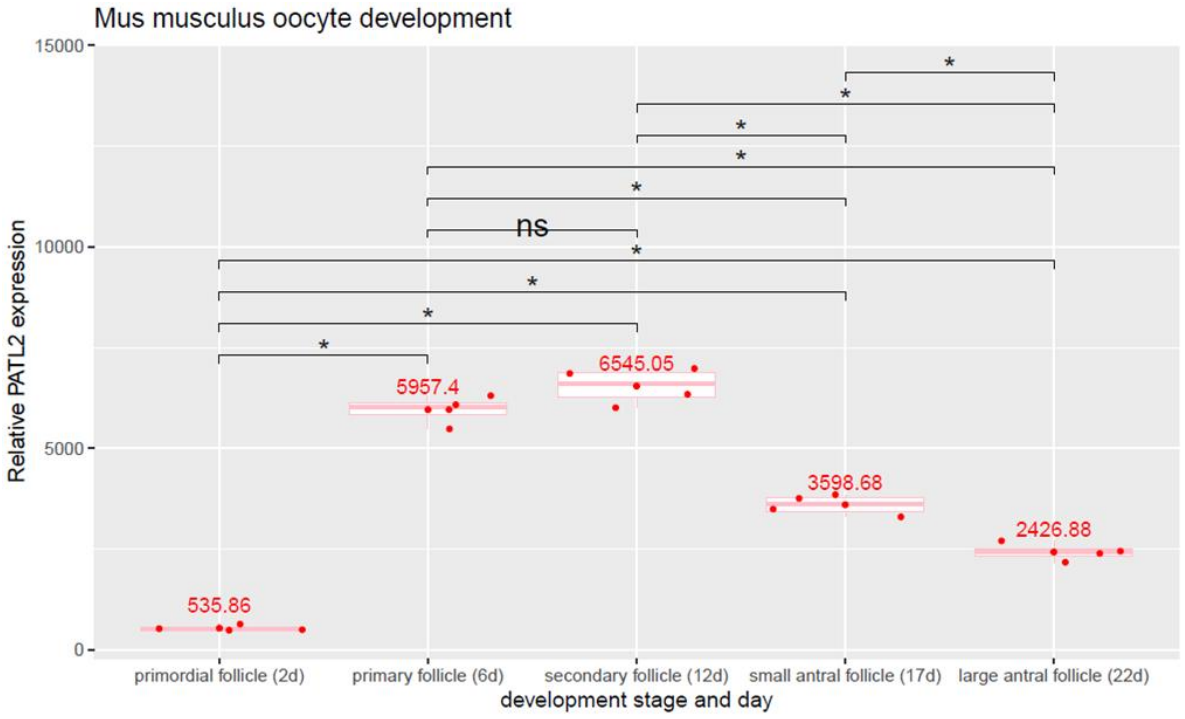

Figure 1. Relative *PATL2* mRNA expression in oocytes from different follicular developmental stages (from primordial follicle stage to large antral follicle stage) in mice. *PATL2* transcript leves at different follicular developmental stages in mice. ns (non-significant): $p > 0.05$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$. Mean expression values were shown in red on boxplots. Data was obtained from GSE3351 dataset (oocytes collected from ovary by follicle stage).

PATL2 expression levels during preimplantation embryo development

Further analysis revealed that *PATL2* transcript levels were analyzed during preimplantation embryo development using GSE1745 dataset, and it was found that *PATL2* mRNA expression is lower in 1-cell embryo compared to oocyte (Figure 3). Similarly, its expression decreases gradually from 1-cell embryo stage to 8-cell embryo stage, then increases in blastocysts to the levels comparable to 1-cell embryo stage, during mouse preimplantation embryo development (Figure 3). However, *PATL2* expression is lower in blastocysts compared to oocytes (Figure 3).

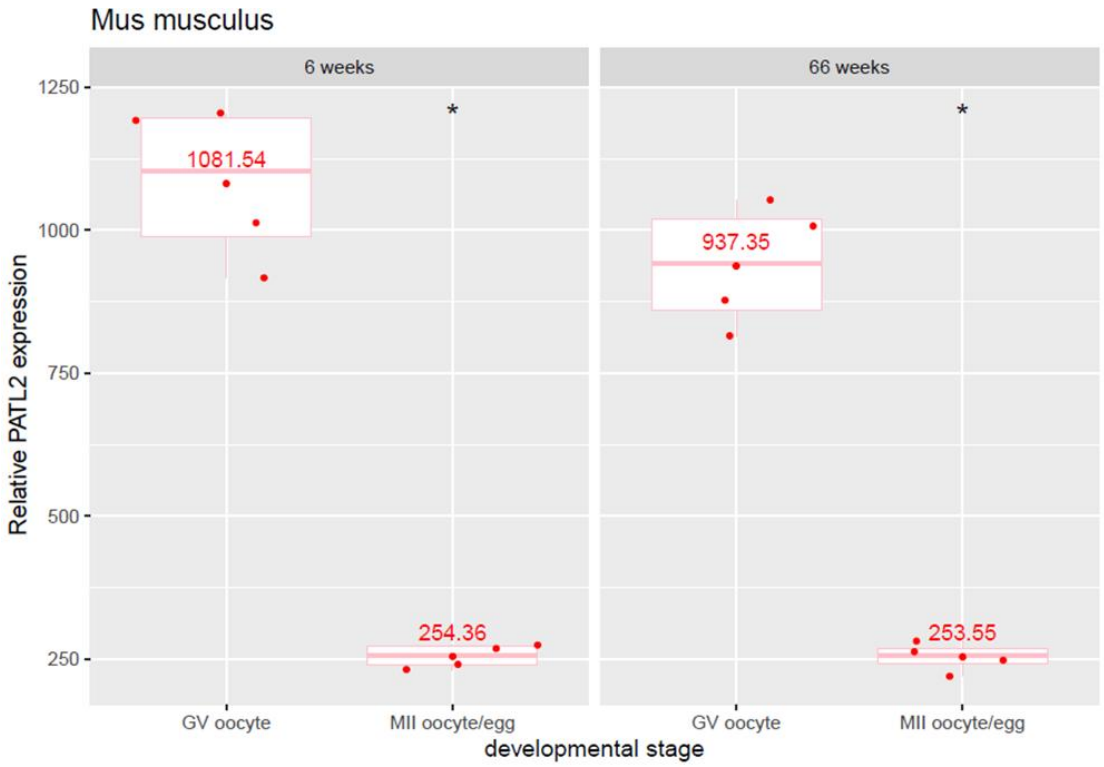

Figure 2. Comparison of PATL2 transcript levels between germinal vesicle (GV) oocytes and (metaphase 2) MII oocytes from young (left) and old mice (right) PATL2 transcript levels between germinal vesicle (GV) oocytes and (metaphase 2) MII oocytes based on age of mice. ns (non-significant): $p > 0.05$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$. Mean expression values were shown in red on boxplots. Data was obtained from GSE11667 dataset (fully-grown GV oocytes).

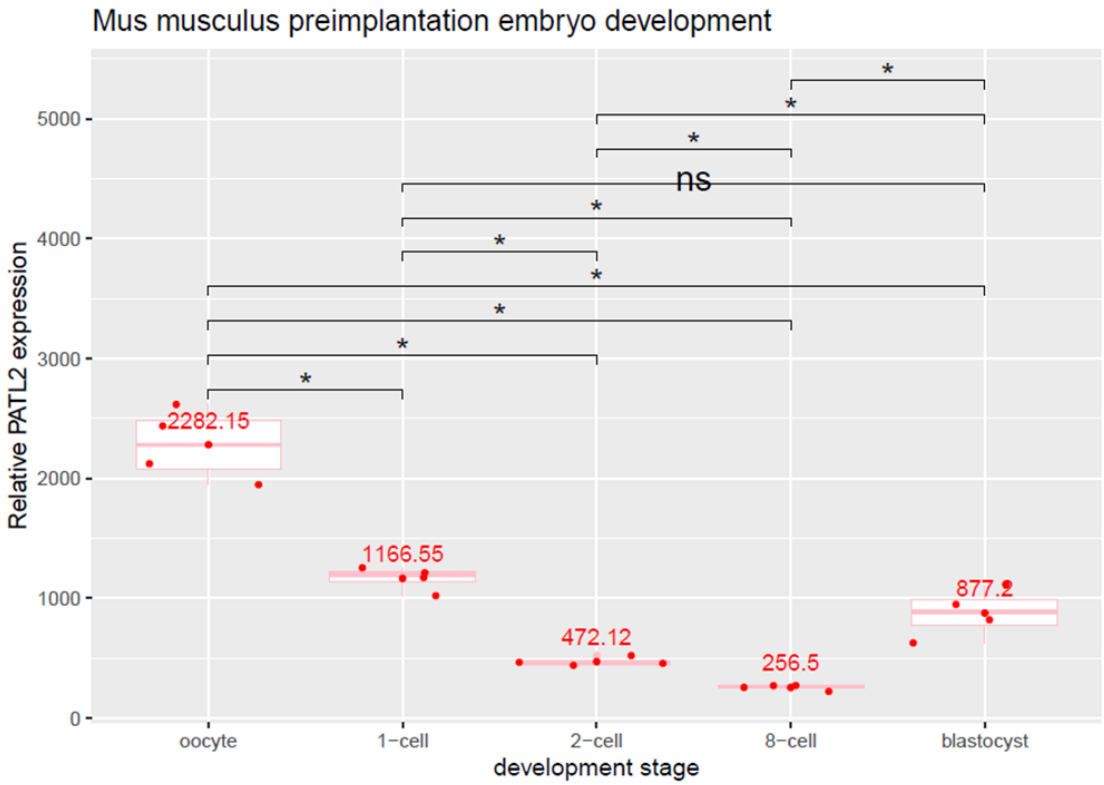

Figure 3. Relative PATL2 mRNA expression during embryo development in mice. PATL2 trancript levels in the course of embryo development in mice. ns (non-significant): $p > 0.05$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$. Mean expression values were shown in red on boxplots. Data was obtained from GSE1745 dataset (preimplantation embryos).

CTCF depletion leads to increased expression of *PATL2* in mouse oocytes

Considering the importance of both CTCF and PATL2 in oocyte maturation, and the importance of CTCF and PATL2 in global transcriptional misregulation in oocytes, the expression of *PATL2* following CTCF depletion was studied in mouse oocytes, using GSE11664 dataset. It was found that CTCF−depleted mouse oocytes have higher expression of PATL2 compared to WT oocytes (p = 0.0083) (Figure 4). Therefore, it can be hypothesized that the negative influence of CTCF depletion on oocyte growth might be mediated, at least in part, by increased levels of PATL2, which are also shown to be associated with oocyte maturation arrest and the deregulation of highly relevant genes involved in oocyte maturation and early embryonic development.

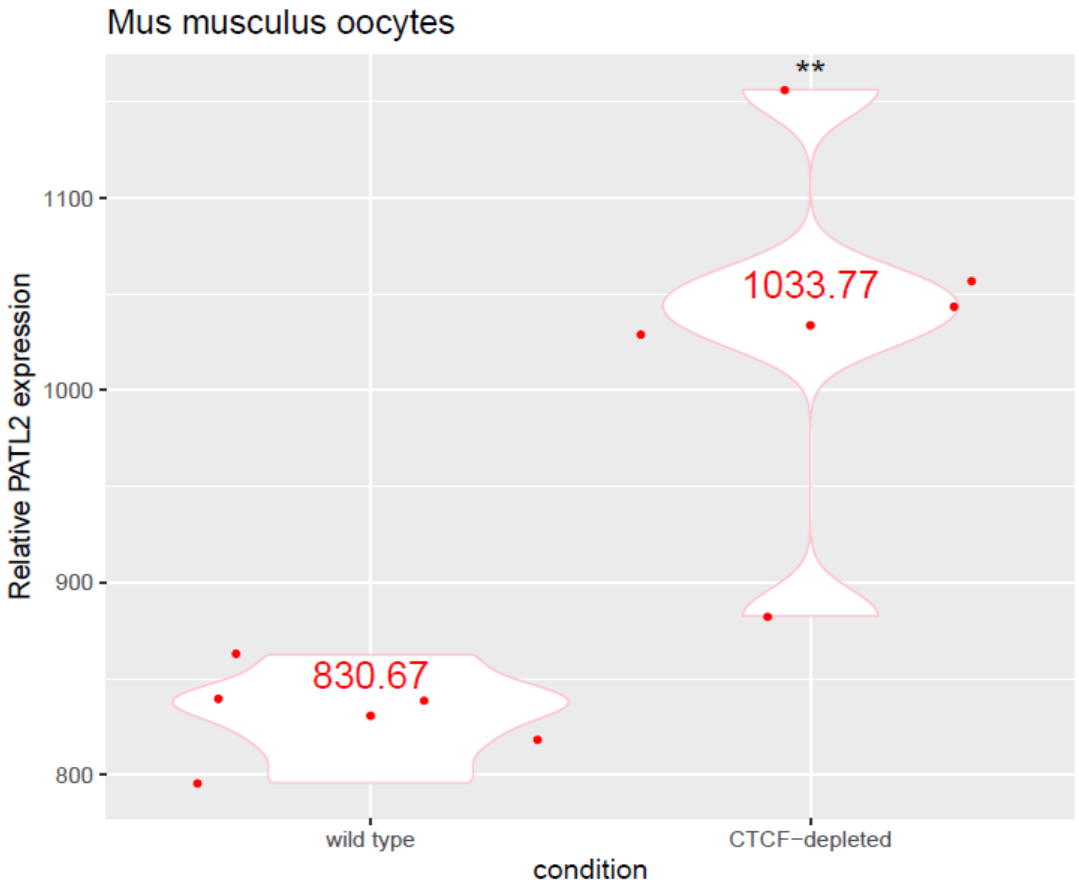

Figure 4. Relative PATL2 transcript levels between WT (wild type) and CTCF-depleted oocytes in mice. PATL2 mRNA levels between WT (wild type) and CTCF-depleted oocytes in mice. ns (non-significant): $p > 0.05$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$. Mean expression values are shown in red on violinplots. CTCF: CCCTC-Binding Factor. Data was obtained from GSE11664 dataset (CTCF-depleted mouse oocytes).

Discussion

Particular *PATL2* mutations in humans cause oocyte maturation arrest, resulting in female infertility; and *PATL2* knockout mice show embryonic development arrest.[1-25, 43] *PATL2* gene encodes an RNA-binding protein which functions as a translational repressor in oocyte maturation; therefore, the proper temporal control of *PATL2* expression is essential for normal oocyte maturation, with implications in female fertility.[3,42] Here, it was shown that *PATL2* expression is regulated at the transcription level in oocytes during oocyte development, paralleling the data previously reported at the protein level.[2, 3, 8, 21] In other words, in addition to the previous observation of dynamic changes in PATL2 protein levels in the course of oocyte development, it was found in the present study that *PATL2* transcript levels also change dynamically during this process. It was found that *PATL2* transcript levels peak in oocytes at primary and secondary follicle stages, then decrease at antral follicle stages. Christou-Kent et al. showed by performing IF and confocal microscopy that primordial follicle oocytes produce no detectable fluorescence signal; however, signal intensity for PATL2 increases in oocytes from primary to secondary follicles, becoming weaker in oocytes contained in tertiary/antral follicles.[3] Major increase in PATL2 expression was observed from primordial follicle stage to primary follicle stage in the current study; however, it is observed from primary follicle stage to secondary (pre-antral) follicle stage in Christou-Kent et al. This discrepancy might be due to the fact that *PATL2* transcript (mRNA) levels are compared here, in contrast to protein levels studied in Christou-Kent et al.[3] In terms of both mRNA and protein

expression in mouse oocytes, PATL2 levels decrease from secondary follicle stage to tertiary (antral) follicle stage (Figure 1). Similarly, in terms of both mRNA and protein levels, *PATL2* expression is higher in oocytes from tertiary follicle stage compared to those from primordial follicle stage (Figure 1). Zhang et al. also showed by immunostaining that PATL2 protein level peaks in the oocytes of secondary follicles, supporting our finding at mRNA level.[21] The data in present study suggests the regulation of *PATL2* expression at the transcriptional level in oocytes during follicle development. Christou-Kent et al. also showed that PATL2 protein levels peak in oocytes at secondary follicle stage, and this might suggest that increased *PATL2* mRNA levels at primary follicle stage are reflected at the protein level at the following follicle stage (secondary follicle stage).[3] Both mRNA and protein levels of PATL2 are decreased at antral (tertiary) follicle stage, pointing to a dynamic regulation of PATL2 expression during oocyte development. The reason why oocytes at secondary follicle stage have increased PATL2 protein levels, and how *PATL2* expression is regulated at molecular level during oocyte growth remains to be studied. Further research is required to understand the importance and function of dynamic regulation of PATL2 expression (at both RNA and protein levels) during oocyte development and also to identify specific regulators of *PATL2* expression. For instance, proteins (transcriptional activator or inhibitors) binding to *PATL2* promoter regions in specific oocyte developmental stages are needed to be determined. Besides, post-transcriptional regulators of PATL2 mRNA remain to be identified.

In parallel, it was found that *PATL2* mRNA expression is lower in metaphase 2 (MII)-stage oocytes than in germinal vesicle (GV)-stage oocytes in mice, similar to other studies showing that PATL2 protein levels are lower in MI and MII oocytes compared to GV oocytes.[2, 8, 21] Thus, it can proposed that PATL2 expression during the GV-MII transition might also be regulated at the transcription level, rather than post-transcriptionally, considering both mRNA and protein levels are lower in MII stage oocytes. It should be studied why GC stage oocytes need higher expression of PATL2. Here, it should also be noted that the most of the oocytes with *PATL2* mutations are arrested at the GV stage, suggesting that functional PATL2 is particularly important at this stage, and that it might have a cellular role in oocytes for normal GV-MII transition.[22] Particular *PATL2* variants might also be associated with the disruption of dynamic regulation of PATL2 expression in oocytes, possibly resulting in oocyte maturation arrest. Dysregulation of factors controlling dynamic *PATL2* expression during oocyte growth might also contribute to oocyte maturation arrest.

Cao et al. reported that a typical recurrent mutation in *PATL2* (*PATL2*^{Y217N}) leads to its decreased ubiquitination and degradation, increasing its expression (abnormal PATL2 protein accumulation) in mouse oocytes, resulting in disturbed oocyte maturation (oocyte maturation arrest) and certain morphological defects.[8] In oocytes, the depletion of CTCF, a protein functioning as both a classical repressor and activator of transcription in oocytes, delays the onset of meiosis and decreases meiotic competence.[26] Following fertilization, its depletion delays the second mitotic division, perturbs zygotic genome activation, results in abnormal nuclear morphology and ultimately leads to apoptosis before the blastocyst stage.[26] CTCF depletion causes persistent transcriptional defects (transcriptional misregulation) in mouse oocytes and preimplantation embryos.[26] Finally, it was shown that CTCF−depleted mouse oocytes have higher expression of *PATL2* compared to WT oocytes. CTCF is a mammalian maternal effect gene which influences transcription during oocyte growth, and has important independent roles in meiotic maturation and early embryonic development.[26] CTCF predominantly activates or derepresses transcription in oocytes, and its depletion causes meiotic defects in the egg.[26] Its loss in growing mouse oocytes results in the transcriptional misregulation of many genes, leading to meiotic defects.[26] Similar to the loss of CTCF, in the absence of *PATL2*, expression levels of a number of highly relevant genes participating in oocyte maturation and early embryonic development are deregulated.[3] Therefore, it can be hypothesized that certain defects in oocytes due to the loss of CTCF might be contributed by the misregulation of *PATL2* expression, which is suggested to be important for normal oocyte maturation. Based on the findings in the present study, *PATL2* expression is tightly controlled during oocyte growth, any factor dysregulating the proper temporal control of *PATL2* might potentially lead to defects in oocyte maturation. Here, please also note that both genes are mammalian maternal effect genes (MEGs) which are present in oocytes and required for early embryonic development.[27]

Study Limitations

Mechanistic details of how PATL2 transcript levels are regulated during oocyte maturation and embryo development should be better understood. Transcriptional or posttranscriptional regulation mechanisms at play need to be determined since the current study only provides data on the changes at the transcript levels but not on the specific regulators functioning in this time-dependent control of PATL2 gene expression. In addition, transcriptomics datasets with larger sample sizes are needed to be constructed to better understand dynamic PATL2 regulation during oocyte maturation and embryo development, since datasets used in the present study have relatively small sample sizes. Moreover, single-cell RNA sequencing (scRNA-Seq) / single-nucleus RNA-Seq datasets or single-cell proteomics data will be more valuable in this respect to understand the dynamic PATL2 regulation in a specific oocyte.

Conclusion

Combined, data in the present study suggest that *PATL2* expression is regulated at the transcriptional level during oocyte growth and maturation, and a better understanding of factors regulating temporal *PATL2* expression during these processes and of cellular consequences of its dysregulation in terms of oocyte maturation arrest and female infertility is needed. It is of high importance considering the critical impact of *PATL2* variants on female fertility in humans.

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Compliance with Ethical Standards

Not applicable.

Conflict of Interest

The author declares no conflicts interests.

Author Contributions

CB: conceptualization, hypothesis, study design, data analysis and visualization, writing first and final drafts.

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