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RETRACTED - Cell transcription dependent on Wingless-type (Wnt)/beta-catenin in the rat estrous cycle stages

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ABSTRACT

Objectives: We aimed to evaluate how T Cell Factor 7 Like 2 (TCF7L2) and Lymphoid Enhancer Factor-1 (LEF-1), which regulate cell transcription, regulate implantation in the endometrium.

Methods: Female rats were determined according to the estrous cycle. The obtained uterine tissues were taken for immunofluorescence staining.

Results: In estrous, LEF-1 and TCF7L2 showed localization in perimetrial-myometrial connective tissue. Of all the signaling molecules, the TCF7L2 molecule is the only one that is expressed. Non-expressed TCF7L2 in the uterine epithelium showed strong immunolocalization in the perimetrial myometrial connective tissue and endometrial basal stroma area. LEF-1 was mostly expressed in the metaestrus phase in the areas of gland epithelium.

Conclusions: TCF7L2 and LEF-1 play a critical role in cell proliferation, differentiation and transcription by regulating the activation of the Wnt signaling pathway in endometrial cells. These findings help us to understand the role of TCF7L2 and LEF-1 in the provision of endometrial homeostasis and in the implantation process.

Keywords: Cell transcription, implantation, rat, T cell factor, lymphoid enhancer factor

During implantation, many signaling molecules are known to play an important role in communication between the blastocyst and the receptive endometrium. In mammals, implantation is a complex and not yet fully understood process involving cellular, hormonal and molecular factors originating from the embryo and endometrium [1, 2]. Successful implantation is possible with precisely arranged reciprocal signaling between the implanted blastocyst and the recipient uterus. Meanwhile, it is defined as a series of processes that involve the embryo first settling in the decidua and then reaching the mother's circulatory system and feeding the placenta. A complex set of dialogue takes place between the endometrium and the embryo through growth factors, hormones, adhesion molecules, cell transcription molecules, and prostaglandins. Thanks to these factors, the embryo adheres to the epithelium, moves towards the basement membrane and invades the stroma. Cellular transcription occurs through various signaling pathways [3]. From these pathways, the Wingless-type (Wnt) signaling pathway plays an important role in the self-renewal of adult cells, cell adhesion, and control of the transcription of target cell genes. In the embryonic period, cell polarity plays a critical role in proliferation, differentiation and cell migration [4]. There are extensive studies in the literature on the Wnt signaling pathway and diseases caused by changes in the

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molecules working in this pathway. With this abnormal expression, the transcription of genes that cause various diseases and cancers takes place [3, 5, 6]. With this activation, both the transcription of proteins working in the signaling pathway takes place and the transcription control of many genes that play an important role in proliferation, cell cycle and differentiation processes is provided [7, 8]. T Cell Factor 7 Like 2 (TCF7L2) and Lymphoid Enhancer Factor-1 (LEF-1) is a family of DNA-binding transcription factors and an important component of β-catenin-mediated gene regulation [9]. Wnt signaling is thought to be effective through interactions between β-catenin and members of the transcription factors LEF-1/TCF7L2 family. LEF-1/TCF7L2 transcription factors mediate a nuclear response by Wnt signals by interacting with β-catenin. Other cellular events that increase the stability of the Wnt signal and β-catenin lead to transcriptional activation with β-catenin and LEF-1/TCF7L2 proteins. In the absence of Wnt signaling, LEF-1/TCF7L2 proteins suppress transcription. LEF-1/TCF7L2 transcription factors can also interact with other cofactors and play a role in the assembly of multiple protein enhancing complexes, which may allow the integration of multiple signal transducing pathways. Stabilized β-catenin translocates into the nucleus, binds to LEF-1/TCF7L2 factors, and regulates interactions between LEF-1/TCF7L2 and nucleus suppressor proteins, a process that activates Wnt target genes [10]. TCF7L2 regulates the expression of genes required for embryo implantation via the Wnt/β-catenin signaling pathway. In this process, it controls critical biological events such as proliferation, differentiation, and migration of cells. The function of TCF7L2 is crucial for successful implantation. Therefore, disruption of these mechanisms may be associated with implantation failure, miscarriage, or other reproductive disorders [10].

Implantation of blastocyst in rats, i.e. placement, binding and subsequent invasion of the trophoblast into the uterine lumen epithelium, is an important process that requires complex biological communication between fetal and maternal tissues. One of the most critical factors for implantation is that blastocyst activation is synchronized with uterine receptivity; the other is controlled by ovarian steroid hormones [11]. In rats, estrogen is essential for proliferation and differentiation of the luminal and glandular epithelium of the uterus, while the coordinated action of estrogen and progesterone promotes stromal cell differentiation. Although the factors driving blastocyst activation are not yet fully understood, various signaling molecules that prepare the uterus for blastocyst implantation are thought to be cell transcription factors [11]. Considering that Wnt signaling plays an important role in embryonic development, it may not be surprising that this particular pathway plays a role in blastocyst activation, implantation, and decidualization as well as uterine growth in mice [12]. Studies have also shown that estrogen upregulates the β-catenin-dependent transcription factors TCF7L2 and LEF-1 independently of the estrogen receptor [13]. Interestingly, hormones trigger the physical interaction of ERa with activated LEF-1/TCF7L2-3 and this interaction directs it to target genes dependent on estrogen and Wnt signaling, suggesting that cross-talk between estrogen and Wnt may be critical for endometrial functions [13]. The attachment of blastocyst has been shown to induce TCF7L2/β-catenin-dependent signaling in circular smooth muscle cells of the myometrium and in the uterine epithelium at the implantation site [14].

In this study, we used immunofluorescence staining method to reveal the function of TCF7L2, LEF-1 proteins in tissues in the estrus cycle in the rat endometrium. Our results suggest that cell transcription plays a central role in coordinating the uterine-embryo interactions required for implantation of TCF7L2 and LEF-1 with the luminal epithelium at the site of possible implantation.

METHODS

Experimental Groups

For this study, 5 adult female Wistar albino rats, 6-8 weeks old and weighing between 220 and 250 grams, were obtained from the Animal Laboratory of Cumhuriyet University (Sivas, Turkey). The animals used in the study were the group in which a normal estrous cycle was provided at room temperature, with 12-hour light-12-hour dark periods, without pregnancy. The animals considered to have entered a normal estrous cycle were given 3 mg/kg Xylazine HCL + 90 mg/kg Ketamine HCL intraperitoneally on the 1st, 2nd, 3rd and 4th days (diestrous, proestrous, estrous, metaestrous) after the 5th day and for all animals every day, and the uterine tissues were taken under anesthe-

sia with appropriate methods for examination. Routine follow-up protocols were applied for immunofluorescence examinations to demonstrate LEF and TCF7L2 proteins. Sections taken for microscopic evaluation were evaluated using an Olympus BX51 (Japan) brand microscope and photographs were taken from appropriate areas.

Tissue Preparation

Uterine tissues taken after euthanasia were fixed in 10% buffered neutral formalin for at least 48 hours and in 4% paraformaldehyde at +4 degrees for 24 hours. After dehydration with increasing grades of ethanol using a tissue tracking device, they were cleared with xylene and blocked in paraffin.

Immunofluorescence Staining Protocol

After the 3-4 µm serial sections taken from the tissue samples embedded in paraffin were kept in the oven for 1 night, deparaffinization was performed in Xylol. Epitopes were released in 10 mM sodium citrate buffer (pH=6) at maximum power and 550W, respectively, in the microwave oven twice for 5 minutes. Pappen (Daido Sangyo Co., Ltd. Tokyo, Japan). The sections were washed in washing solution (PBS-Triton X-100) twice for 3 minutes. The sections were incubated in SuperBlock (Sky Tech Lab, USA) solution at room temperature for 30 minutes to prevent nonspecific transport of immunoglobulin. (Serum Blocking). The sections were incubated overnight with primary antibodies in a humid dark environment at TCF7L2 and LAEF-1 +4 degrees. It was washed in washing solution (PBS-Triton X-100) 4 times for 3 minutes each. Secondary antibody Goat Anti-Rabbit IgG H&L (Alexa Flour 488): ab150077 abcam) was incubated at room temperature for 1 hour in a humid environment. It was washed in washing solution (PBS-Triton X-100) 4 times for 3 minutes each. Core staining was performed with 0.5 ug/ml DAPI (Sigma, USA) at room temperature for 10 minutes. It was washed in washing solution (PBS-Triton X-100) for 5 minutes. The closure was done with the closure medium.

RESULTS

Preparations prepared following routine protocols were stained with hematoxylin-eosin in the first stage and then examined under a light microscope. In the second stage, immunofluorescent stains containing LEF-1 and TCF7L2 antibodies were applied to the preparations.

Estrous Cycle (Hematoxylin-Eosin)

Proestrous phase

It was observed that the lumen was filled with fluid. It was determined that mitotic activity continued in the epithelial cells consisting of single-layered columnar cells. In the following process, it was observed that the columnar cells gradually increased in size and transformed into single-layered high columnar cells (Fig. 1. G and H)

Estrous phase

In light microscopic examinations, it was observed that the uterine lumen distension reached the maximum level. In aoddition, a significant difference in size was

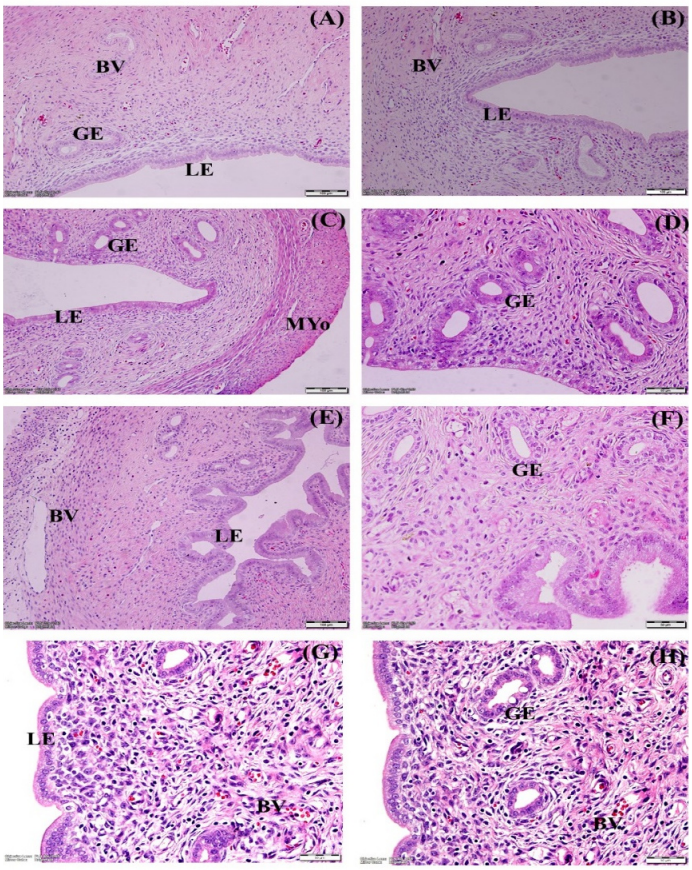

Fig. 1. Estrous cycle stages: Proestrus (G-H), Estrus (E-F), Metaestrus (C-D), Diestrus (A-B). UL=uterine lumen, UE=uterine epithelium, BE=gland epithelium, L=leukocyte, KD=blood vessel.

Table 1. TCF7L2 and LEF-1 immunolocalizations in estrous cycle stages

Protein	Endometrial region\Estrous cycle	Proestrous	Estrous	Metaestrous	Diestrous
LEF-1	PMC	-	++	++	+
	Myometrium	-	++	+	-
	Luminal Epithelium	++	+++	+	+
	Glandular Epithelium	No gland	No gland	+++	++
	Endometrial basal stroma	+	++	++	+
	Blood vessel	++	+++	++	+
TCF7L2	PMC	+++	+++	++	++
	Myometrium	+	+	++	++
	Luminal Epithelium	+	-	-	-
	Glandular Epithelium	No gland	No gland	+++	-
	Endometrial basal stroma	++	+++	++	+++
	Blood vessel	++	++	+++	+++

TCF7L2=T Cell Factor 7 Like 2, LEF-1=Lymphoid Enhancer Factor-1, PMC= Perimetrial myometrial area

detected in the uterine epithelial cells arranged in clusters. No leukocytes were found in the uterine preparations in the estrus stage (Fig. 1. E and F)

Metaestrous phase

While luminal epithelium and gland vacuolar degenerations continued, mitotic activity was observed to have started again. In addition, dominant leukocytes were observed in metaestrus. A decrease was observed in blood vessels and gland epithelium (Fig 1. C and D).

Diestrous phase

The uterus has cuboidal-prismatic epithelial cells. In this stage, the lumen of the uterus is observed to expand. In the uterus in dietrus, the epithelial cells have atrophic and collapsed features. While sparse degenerative cells are observed in the endometrial glands, stromal edema is detected in the stroma region. It has been determined that endometrial regeneration has started again (Fig 1. A and B).

Expression of LEF-1 and TCF7L2 during Estrous Cycle Stages

This group estrous cycle was examined in 4 basic stages (diestrous, proestrous, estrous and metaestrous) based on histological findings. Immunofluorescent dyes containing LEF-1 and TCF7L2 antibodies were applied to the preparations prepared following routine protocols, and the immunolocalization levels of these molecules in perimetrial-myometrial connective tissue, myometrium, uterine epithelium, gland epithelium, stroma, and blood vessels were examined under an immunofluorescent microscope. cake is shown in Table 1.

Proestrous

TCF7L2 molecule was expressed in all regions in the proestrus phase, which constitutes the 1st stage of the estrus cycle (Fig. 2. C and D). The most localization occurred in the perimetrial myometrial region (Fig. 2. C). Blood vessels showed a moderate immune reaction in the form of endothelials. The lowest level of expression belongs to the luminal epithelium. Immunolocalization levels of the LEF-1 molecule were observed in the highest endometrial basal stroma region. No localization was observed in the myometrium and perimetrial myometrial area. The expression level of the luminal epithelium was expressed as strong (Fig. 2. A and B).

Estrous

While estrous shows strong expression in TCF7L2, perimetrial myometrial area and endometrial basal stroma in the estrus stage, there is no expression in the luminal epithelium (Fig. 3. C). While LEF-1 was strongly immunolocalized in endothelials, TCF7L2 showed moderate expression (Fig. 3. A). The

highest localization of LEF-1 was observed in the luminal epithelium (Fig. 3. B).

Metaestrous

Uterine epithelium showed the least immunoreactivity compared to almost all stages of the estrous cycle, while strong localization was observed in the gland epithelium areas. Very little expression was observed in the endometrial basal stroma areas compared to the subluminal stromal regions (Fig. 4. A, B, C and D). It was observed in the metaestrus phase in the gland epithelial areas where LEF-1 protein was most expressed throughout the estrous cycle (Fig. 4. A and B). The TCF7L2 molecule is not localized in the uterine epithelium (Fig. 4. C and D). Moderate immunolocalization occurred in the endometrial basal stroma. While moderate strong expression was observed in blood vessels in certain areas, unlike other molecules, moderate strong localization was observed in perimetrial myometrial connective tissue areas. The level of immunolocalization of TCF7L2 along the myometrium-endometrium border is moderate.

Diestrous

Poor expression was observed in the uterine epithelium, gland epithelium, subluminal stroma and endometrial basal stroma of LEF-1. In the blood vessels and blood vessel stroma, the expression is quite weak in the same way (Fig. 5. A and B). Localization of the molecule in the perimetrial-myometrial connective tissue region is poor. The TCF7L2 molecule, on the other hand, is not expressed in the cytoplasm of the uterine epithelium (Fig. 5. C). It has been determined that TCF7L2 shows strong expression in blood vessels (Fig. 5. D). It was determined that only TCF7L2, one of the signaling pathway molecules, was expressed in the perimetrial-myometrial connective tissue area of the uterus, and the localization intensity was moderate. Similarly, immunolocalization of the molecule in the myometrium region occurred at a moderate level (Fig. 5. C).

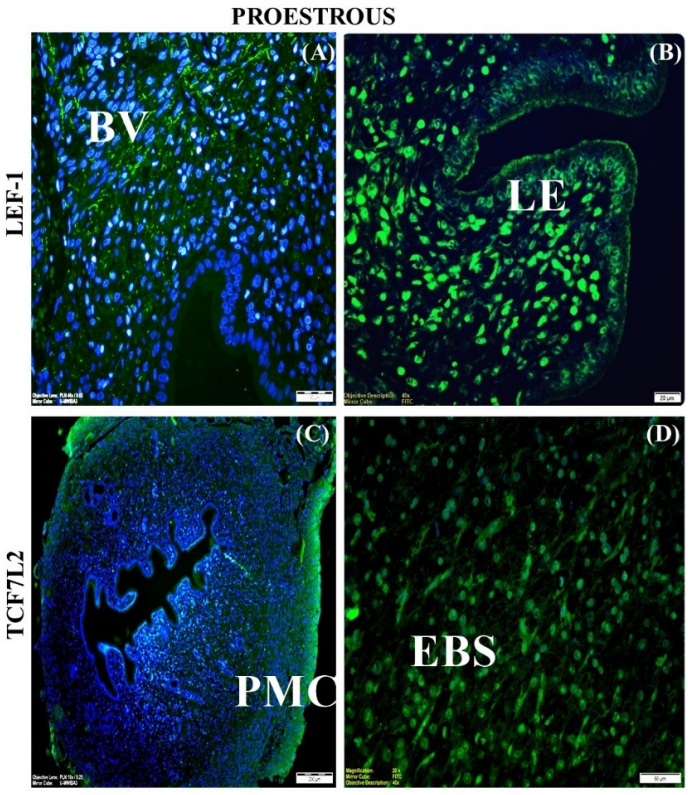

Fig. 2. Immunolocalization of LEF-1 and TCF7L2 in the proestrus phase. BV=Blood vessel, LE=Luminal epithelium, PMC=Perimetrial myometrial area, EBS=Endometrial basal stroma.

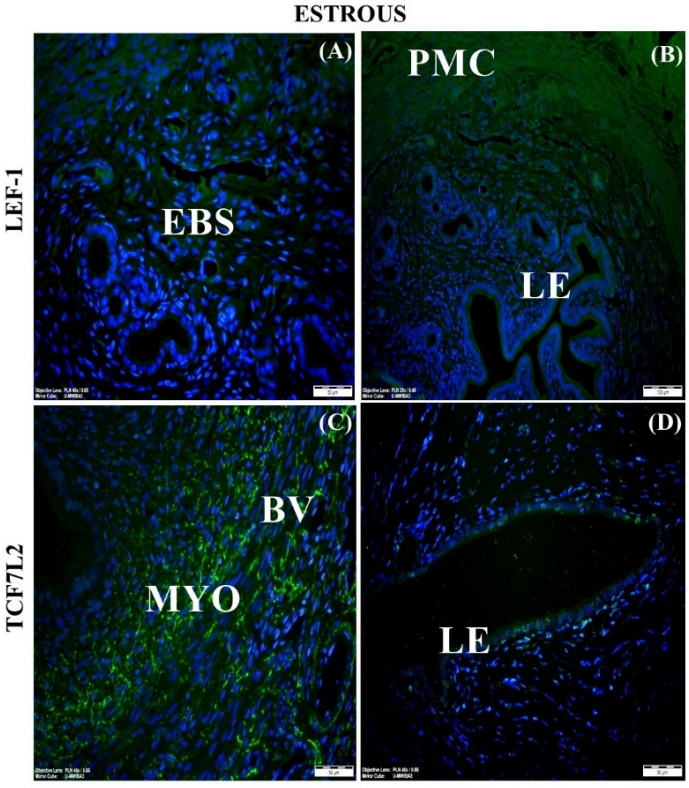

Fig. 3. Immunolocalization of LEF-1 and TCF7L2 in the estrus stage. BV=Blood vessel, LE=Luminal epithelium, PMC=Perimetrial myometrial area, EBS=Endometrial basal stroma, MYO=Myometrium.

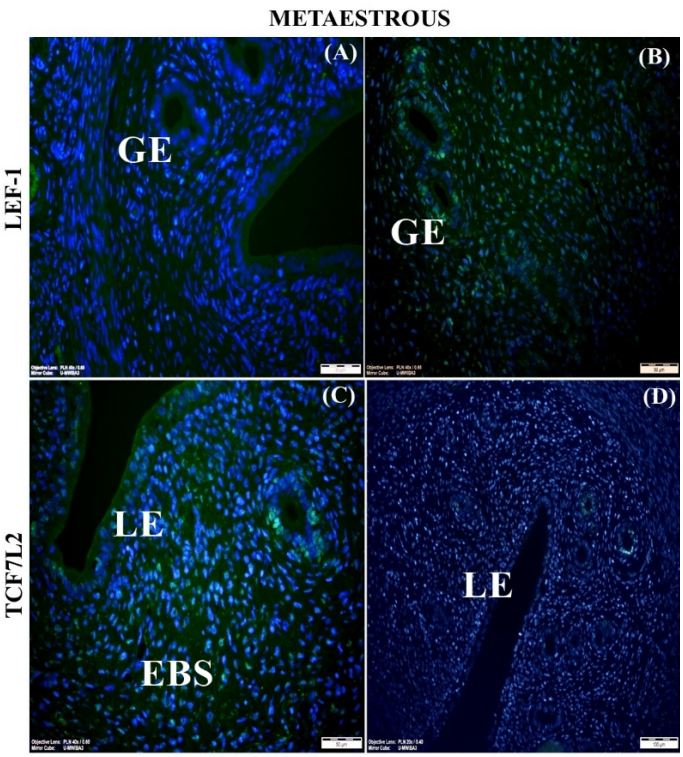

Fig. 4. Immunolocalization of LEF-1 and TCF7L2 in the metaestrus phase. BV=Blood vessel, LE=Luminal epithelium, PMC=Perimetrial myometrial area, EBS=Endometrial basal stroma, GE=Gland Epithelium.

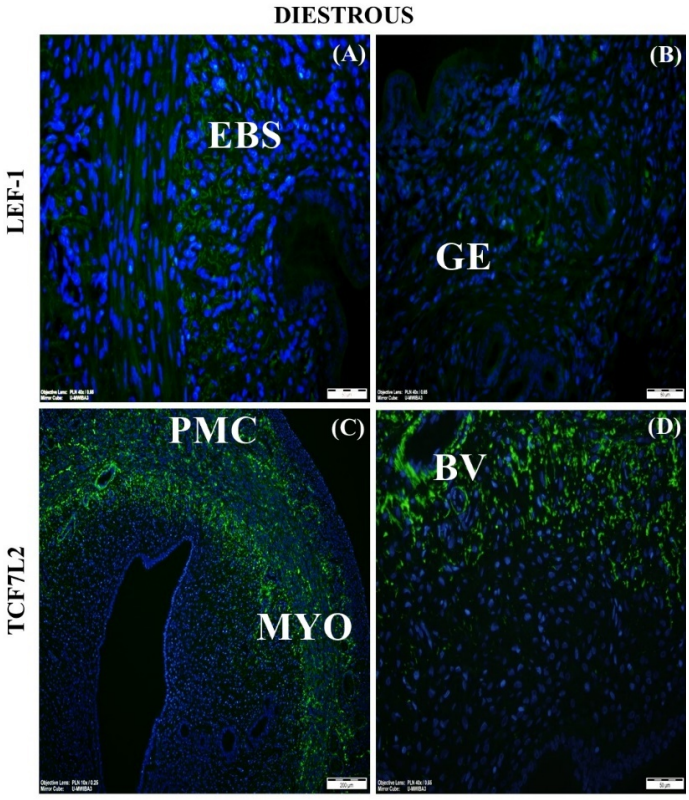

Fig. 5. Immunolocalization of LEF-1 and TCF7L2 in the diestrus phase. BV=Blood vessel, LE=Luminal epithelium, PMC=Perimetrial myometrial area, EBS=Endometrial basal stroma, MYO=Myometrium.

DISCUSSION

Although the embryo-uterine interaction is known to play an important role in facilitating implantation, it is known that several signaling pathways are specifically activated in the uterus in response to signals secreted by the blastocyst. Our results show that blastocyst activates the Wnt-dependent β-catenin signal in the uterine endometrium and activation of this pathway is necessary for implantation. These findings suggest that this paracrine signaling mechanism plays a central role in coordinating the uterus-embryo interactions required for implantation.

The TCF7L2 molecule is a Wnt/beta-catenin-dependent protein. Binding of the Wnt/protein to the receptors initiates signal transmission in the cell membrane and causes the disintegration of the destructive complex present in the cytosol. As a result of the dispersion of this chemical complex, the β-catenin, which is freed from the phosphorylation effect, is introduced into the nucleus, where a direct signal is transmitted from the cytoplasm to the nucleus [15]. Biomolecules involved in the nuclear activation of the Wnt/β-catenin signaling pathway were identified as TCF7L2)/LEF-1 transcription factors. This mechanism is explained as follows: TCF7L2 transcription factors are found in the nucleus and bind to DNA and activate gene transcription. Therefore, they are vital in many cellular processes [16]. The C-terminal ends of TCF7L2/LEF-1 transcription factors have a DNA binding site consisting of the sequence "AGATCAAAGGG" that can bind to a specific region of DNA [17]. This area is called high-mobility group (HMG). In the nucleus, these transcription factors need to bind to the β-catenin protein in order to be activated. Therefore, β-catenin is known to be a coactivator of TCF7L2/LEF transcription factors [18, 19]. The structure formed by this binding of beta-catenin is called "β-catenin-TCF7L2/LEF1 transcription complex" and it has been determined that this complex will

bind to DNA to form target genes [20, 21]. In a study conducted in 2007, the working mechanism of TCF7L2/LEF transcription factors argues that while the signaling pathway of Wnt beta-catenin is inactive, the transcription factors should also be inactive. He said that beta-catenin, which is broken down by the destructive complex effect that is active when the signal pathway is inactive, cannot enter the nucleus and cannot activate them because beta-catenin cannot enter the nucleus and cannot bind to transcription factors. As a result, it has been stated that genes inhibit transcription and various other proteins such as Groucho/TLE (Transducin-like-Enhancer of split) and C-terminal binding proteins (CtBP) in the nucleus also bind to TCF7L2/LEF transcription factors [22]. This binding allows to keep transcription factors inactive. Therefore, these proteins are known as transcription inhibitors.

The TCF7L2 protein, known as the T cell factor, increases cytosolic accumulation that inhibits the degradation of β-catenin and promotes the binding of TCF7L2 family transcription factors to the lymphoid-strengthening binding factor, LEF-1 [16, 23]. In unstimulated cells, they act as transcription inhibitors in other preservatives such as Lef/TCF7L2 groucho transducin-like (TLE) family proteins [24]. Together with these properties, these receptors provide an activation site for TCF7L2/LEF upon WNT activation. Cyclin, which is involved in active TCF7L2/LEF cell proliferation and invasion, induces the expression of target genes such as D1 [16]. Pollheimer *et al*. [25] associated it with the synthesis of TCF7L2 or TCF7L2-4 in the formation and differentiation of extravillus trophoblasts or trophoblasts [25]. Regardless of these studies, in our studies on rat endometrium, the moderate and strong immune reaction of rats in all four stages throughout the estrus cycle, especially in the endometrial basal stroma areas, supported the presence of a transcription in the nuclei of the cells located here, but the fact that it is not localized in the uterine epithelium in the estrus, metaestrus and diestrus periods suggested that factors that are not yet known may be effective. The staining of the TCF7L2 molecule in the nucleus rather than in the cytoplasm shows that it is a transcription in the nucleus, and it is thought that this result may be due to the differentiation in the nuclei of the decidual cells. LEF, on the other hand, initiates the recognition of the wnt ligand with transmembrane receptors on the cell surface and the cascade that will redirect it to the nucleus by stabilizing the normally unstable armadillo repeat protein, beta catenin. The Lef protein interacts with the Lef/TCF7L2 DNA binding protein in the beta-catenin nucleus, which has increased stabilization and amount in the cell depending on the canonical wnt signal with the TCF7L2 protein [2]. In a study on LEF-1 protein and endometrial carcinomas, mutations of the CTNNB1 gene that occur in 12-25% of endometrial carcinomas have typically shown that beta-catenin causes an increase in cytoplasmic and nuclear accumulation, which subsequently leads to activation of LEF-1 and TCF7L2 family members. This relationship between activated LEF-1 protein and mutated beta-catenin has given a clue that LEF-1 may cause irregularity of molecules in endometrial cancer cases [2, 26]. Wnt suggests that beta-catenin will contribute to the regulation of uterine growth on LEF-1 of the signaling pathway, as well as to the normal development and function of the uterus [27]. In a study by Shelton *et al*. [28] on endometrial gland formation in mice, they observed that LEF-1 protein may be expressed during uterine development and estrus period. They reported that the Lef/TCF7L2-dependent signaling of the LEF-1 expression Wnt/beta-catenin signaling pathway during uterine development had a delicate regulation during the estrous cycle in mice. They observed that there may be changes in cell proliferation in the glands during the estrous cycle. In the same study, they showed that the expression of LEF-1 in the uterus was effective in both the development and the formation and control of the endometrial glands, and in the absence of LEF-1, despite the presence of a normal endometrium, it resulted in the formation of an unsuccessful uterine gland. When knockout was characterized in the LEF-1 study in mice, it was shown that these mice lacked mammary glands and epithelial mesenchymal interactions, for example, in hair follicles [29]. There have not been many studies on the presence of LEF-1 in estrus and its period, but it is known that LEF-1 is a beta-catenin-dependent transcription factor in the Wnt signaling pathway. During estrus cycle periods, LEF-1 protein was expressed at the same level in almost all stages. It has been confirmed that the estrous cycle is effective in the development of the glandular gland, especially

during the metaestrus period, by being expressed in the glandular epithelium. It was thought that immunolocalization in the gland epithelium during the metaestrus period may be due to the variability of progesterone and LH levels. In the literature, it is observed that it helps the development of the uterine gland and that the estrous cycle is mostly expressed during the proestrus period, and the observed LEF-1 protein gains accuracy by helping the development of the gland with our findings, but it does not coincide with the stronger immune reaction of the gland epithelium in the metaestrus of the estrous cycle compared to the proestrus period.

CONCLUSION

It can be concluded that TCF7L2 and LEF-1 work together in the Wnt/β-catenin signaling pathway to regulate the cellular and genetic processes required for the successful implantation of the embryo into the uterine wall, and therefore the interaction of these molecules plays a critical role in the success of implantation. As a result, it is seen that the transcription in the cell nucleus occurs by beta-catenin-dependent TCF7L2/LEF-1 proteins for successful implantation and the development of the uterine epithelium and uterine glandular glands.

Authors' Contribution

Study Conception: TD; Study Design: TD; Supervision: TD; Funding: TD; Materials: TD; Data Collection and/or Processing: TD; Statistical Analysis and/or Data Interpretation: TD; Literature Review: TD; Manuscript Preparation: TD and Critical Review: TD.

Ethics Approval

This study was approved by the Sivas Cumhuriyet University Animal Experiments Local Ethics Committee (Decision no.: 12, Date: 27.01.2017)

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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RETRACTION NOTE:
This study has been retracted at the author's request