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Original Article

Co-localization of galectin-3 and integrin β3 at mouse maternal-fetal interface during early embryo implantation

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Abstract: Galectin-3 (gal-3), a β-galactoside-binding protein, plays a role in the regulation of endometrial cell proliferation and adhesion and has been recognized as an important factor in endometrial receptivity. This study aimed to investigate the spatial expression pattern of gal-3 and integrin β3 in the uterus during embryo implantation and the co-localization of gal-3 with its ligands at the implantation and inter-implantation sites. We tested whether the embryo itself affects the expression and distribution of gal-3 in the uterus and we used uteri from a pseudo-pregnant mouse model were used as a control. Real-time PCR and Western blotting analyses showed that mRNA and protein of gal-3 and integrin β3 expression in the implantation site were significantly higher than those in the inter-implantation site, and gal-3 expression was also strong in the pseudo-pregnant endometrium. Immunofluorescence data indicated that the expression of gal-3 and integrin β3 was enriched in the luminal epithelium, particularly at the implantation site. However, strong FN expression was observed in the stroma and blastocysts with a slight difference between the two sites. Moreover, con-focal analysis revealed strong co-localization of gal-3 and integrin β3 while only sparse co-localization of gal-3 and FN in the luminal epithelium at the maternal-fetal interface. In conclusion, high expression and co-localization of gal-3 and integrin β3 is found at the maternal-fetal interface, suggesting that the interaction between gal-3 and integrin β3 at maternal-fetal interface may play an important role in the endometrial receptivity during early embryo implantation.

Keywords: Maternal-fetal interface, galectin-3, integrin β3, fibronectin, co-localization

Introduction

Embryo implantation is an intricate process whereby the developing embryo attaches and embeds in the endometrium, which is the first cross-talk between the embryo and receptive endometrium [1]. Prior to the implantation, the endometrium undergoes complex morphological, physiological and biochemical changes. Successful implantation is not only dependent on the invasive ability of the embryo, but also on the establishment of endometrial receptivity [2, 3]. Many cell adhesion molecules, such as integrins, are well known biomarkers of implantation. These adhesion molecules and other cytokines make the endometrium conducive to embryo implantation [3]. However, the cross-talk at the maternal-fetal interface has not been fully understood.

Galectin-3 (gal-3) is a member of an ancient lectin family. Gal-3 is a novel molecule that contains a long unique N-terminal proline- and glycine-rich domain, which is connected to a conserved carbohydrate recognition domain. Gal-3 is widely expressed in different cell types, such as tumor cells, macrophages, epithelial cells and fibroblasts, and participates in cell proliferation, adhesion, apoptosis and many physiological and pathological processes [4-6]. Previous studies have reported that gal-3 is increased in the mid-secretory phase of the menstrual cycle [7]. Our previous study explored the relationship between gal-3 and endometrial receptivity using suppression substractive hybridization (SSH) [8]. Moreover, our previous *in vitro* studies demonstrated that the expression and secretion of gal-3 from trophoblast and endometrial epithelial cells can be regulat-

ed by 17β-estradiol, progesterone and human chorionic gonadotropin (hCG) [9, 10]. It has been demonstrated that endogenous gal-3 inhibits apoptosis but promotes proliferation of endometrial cells, while exogenous gal-3 plays the opposite role [10, 11], although their precise mechanisms are still elusive.

Integrins, a family of heterodimeric cell surface glycoprotein receptors, are known as gal-3 binding ligands and are involved in the regulation of cell adhesion and trafficking [12]. It is well characterized that integrins play a pivotal role in cell adhesion, migration, organization of the cytoskeleton, and transduction of differentiation signals via interaction with the extracellular matrix, such as fibronectin (FN) and vitronectin [13]. In the endometrium, integrin expression is spatially and temporally regulated throughout the menstrual cycle and early pregnancy [9, 14]. Among different integrins, integrin αVβ3 has been widely regarded as an epithelial marker that indicates opening of the implantation window, which directs the endometrium from a non-adhesive to an adhesive state [15]. Before embryo implantation, integrin αVβ3 relocates to the apical surface of trophoblast cells and is continuously expressed in the endometrial cells to facilitate endometrial cells proliferation and adhesive ability during peri-implantation [16, 24]. Therefore, we speculate there may exist an association between gal-3 and integrin β3 at the maternal-fetal interface during early embryo implantation.

In the present study, we investigated the expression pattern of gal-3 and integrin β3 at maternal-fetal interface and co-localization of gal-3 with its ligands, adhesive markers: integrin β3 and FN.

Materials and methods

Animals and sampling

Sexually mature Kunming (KM) mice (6-8 weeks old, weighing 23-25 g) were purchased from the Shanghai Laboratory Animal Center, Chinese Academy of Sciences. The mice were housed in a temperature- and humidity-controlled room under a 12/12 h light/dark cycle. This study had gotten the permission of research ethics committee at the Obstetrics and Gynecology Hospital, Fudan University.

Female mice were caged overnight with males and the presence of a vaginal plug was considered as day 1 of pregnancy. Under sterile conditions, sacrifice female mice on day 0, day 2, day 4, day 6 and day 8 after the vaginal plug observed (n = 20 in each group) and collect the uterus. To obtain endometrium at the receptive state, pregnant mice (n = 20) were sacrificed on day 5 at 8:00-11:00 a.m. after the injection of 0.1 ml of 1% Chicago blue dye (Sigma-Aldrich Inc., St. Louis, MO, USA) via tail vein. Implantation sites were determined by distinct blue bands. Under sterile conditions, the endometrium from both the implantation site and inter-implantation site in each mouse was collected separately.

To induce the pseudo-pregnant model, female mice (n = 20) were mated with vasectomized males (n = 5). The mice were sacrificed on day 5 at 8:00-11:00 a.m. after vaginal plug presentation and endometrium samples were collected under sterile condition.

In the control group, 20 female non-pregnant mice were sacrificed and endometrium samples were collected.

For real-time PCR and Western blotting analyses, tissues from four groups were rapidly flash frozen and stored at -80°C, while the tissue for immunostaining were fixed in 4% paraformaldehyde for 24 h at room temperature. The tissue from the peri-implantation models was embedded in paraffin blocks for immunohistichemistry while the other for immunofluroscence was embedded in optical cutting temperature (OCT) medium after dehydration in 20% sucrose for 3-4 h and finally stored at -80°C. The study was performed with the permission of the Shanghai Scientific and Technical Committee (license No. 2012-36). All analyses and experiments were performed upon the approval of the research ethics committee at the Obstetrics and Gynecology Hospital, Fudan University.

Real-time PCR

Total RNA was extracted from endometrial tissue from the four groups using the TRIzol (Invitrogen, Life Technologies, Grand Island, NY, USA). The quantity and quality of RNA was assessed by OD_{260} and OD_{280} measurements. A total of 1 μg total RNA was reverse transcribed using the PrimeScript RT reagent kit (Takara, Dalian, China) according to the manufacturer's instructions. The mRNA expression of gal-3 in

four groups was determined by real-time PCR using SYBR Premix Ex Taq (Takara) with the Applied Biosystems 7900 system. Data were collected after each annealing step. β-actin was used as an endogenous control to normalize gal-3 mRNA expression in the four groups. Primer sequences and sizes of the amplified fragments were as follows: Gal-3: 5'-CAGGAAAATGGCAGACAGCTT-3' (sense), 5'-CCCATGCACCCGGATATC-3' (anti-sense); Integrin β3: 5'-GACGGATACTGGCAAAAACG-3' (sense), 5'-CTCAGGCTCTTCCACCACAT-3' (anti-sense). β-actin: 5'-AGATTACTGCTCTGGCTCCT-3' (sense), 5'-CATCTGCTGGAAGGTGGACA-3' (anti-sense). Experiments were performed in triplicate for each sample.

Western blotting

The endometrial tissues were homogenized using cell lysis buffer and the protein concentration was determined using the BCA Protein Assay Kit (Beyotime, Jiangsu, China). Endometrial tissue proteins were separated by 8% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gel and subsequently transferred onto nitrocellulose membranes, then blocked in 5% nonfat milk for 1 h at room temperature. The membranes were incubated overnight at 4°C with primary antibodies, including monoclonal mouse anti-mouse gal-3 (1:1000, Abcam, Cambridge, MA, USA), monoclonal rabbit anti mouse integrin β3 (1:500, Abcam, Cambridge, MA, USA) and β-actin (1:1000, Beyotime, Jiangsu, China) with gentle shaking, followed by incubation with horseradish peroxidase-conjugated secondary antibodies. Signals were detected using the enhanced chemiluminescence assay. The data were analyzed by Quantity One software. Each sample was analyzed in triplicate.

Immunhistochemistry staining

The tissue embedded paraffin blocks were cut into 4-μm sections and mounted on polylysine-coated slides, dewaxed and rehaydated. Then according to our previous publication [18], each endometrial slides were immunostained for gal-3 (1:500, ebioscience). The degree of slides staining was assigned in a blinded manner by two investigators with professional software (ImagePro Plus 6.0). For each sample, 10 random visual filed images at ×400 magnification were selected and scanned, and the average intensity of each sample was analyzed.

Immunofluorescence

The endometrial tissues embedded in OCT were cut into 4-μm sections and mounted on polylysine-coated slides. Tissue slides were washed in phosphate buffered saline (PBS) for 15 min, and blocked in 10% normal goat serum in PBS for 30 min, and then incubated with a mixture of the following primary antibodies: monoclonal rat anti-gal-3 antibody (1:200, Millipore, Billerica, MA, USA) and monoclonal American hamster anti-integrin β3 (1:50, Millipore) or polyclonal rabbit anti-fibronectin (1:50, Abcam) overnight at 4°C. After several washes, the slides were incubated with a mixture of secondary antibodies, including Alexa Fluor 555-conjugated goat anti-rat IgG (1:500, Cell Signaling Technology, Danvers, MA, USA) and FITC-conjugated goat anti-American hamster IgG (1:100, eBioscience, San Diego, CA,USA) or Alexa Fluor 647-conjugated goat anti-rabbit IgG (1:200, Abcam) for 1 h. The slides were washed three times, mounted on glass microscope slides with Vectashield mounting medium with 4',6-diamidino-2-phenylindole (DAPI) (Vector, Laboratories, Burlingame, CA, USA), and examined under a Leica TCS SP5 MP confocal microscope. Image analysis was performed using the software package provided by Image Pro Plus. Experiments were performed in duplicate and repeated at least three times.

Statistical analysis

All results are presented as the mean ± standard error of mean (SEM). One-way ANOVA was performed and least significant difference was applied for post hoc test using Excel (Microsoft). A $P < 0.05$ was considered statistically significant.

Results

Gal-3 expression pattern during implantation period

Recently, gal-3 has been recognized as a endometrial receptivity factor because of its increased expression in the human endometrium during the window of implantation, and our previous study suggests gal-3 knocked down female mice have lower fertility rate; therefore, we used mice from peri-implantation period to show the spatial and temporal expression of gal-3 in pregnant mice.

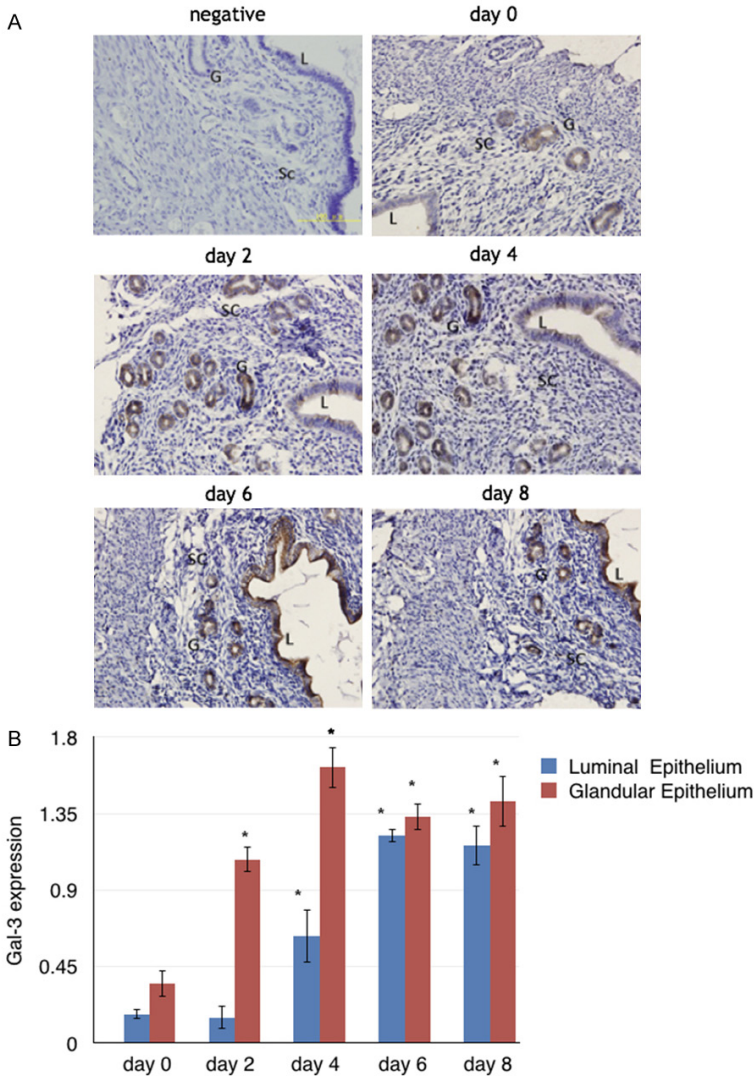

Figure 1. Expression of gal-3 during implantation period, on day 0, day 2, day 4, day 6 and day 8. Control is from non-pregnant mouse at random day, and 3 samples were used for control. Data were analyzed using one-way ANOVA and least significant difference analysis. Experiments were performed in duplicate and repeated at least three times. Bar = 100 μm. (*P < 0.05, compared with day 0. G = gland; L = lumen of uterus; SC = stromal cells).

The results indicated and validated that gal-3 expression began to increase after pregnancy reaching maximum on day 4 in glandular epithelium and day 6 in luminal epithelium (**Figure 1**).

Gal-3 and integrin β3 expression in the endometrium in different groups

Although the dynamic expression-pattern of gal-3 in the mouse endometrium during the peri-implantation period has been reported [18], the expression site of gal-3 in the endometrium is still unknown. In this study, we first compared the expression of gal-3 and integrin β3 mRNA and protein in the implantation site, inter-implantation site, pseudo-pregnant and non-pregnant endometrium. As shown in **Figure 2A**, gal-3 mRNA expression in the implantation site and in the pseudo-pregnant endometrium was significantly higher than that in the inter-implantation site, and the gal-3 mRNA expression in the endometrium of non-pregnant mice was significantly lower than that in the other three groups. Moreover, the strongest gal-3 mRNA expression was observed at the implantation site in the endometrium. The expression pattern of gal-3 protein was completely consistent with its mRNA expression in the four groups (**Figure 2B**, **2C**). As for integrin β3 mRNA and protein expressions (**Figure 2B**, **2C**), they were obviously the strongest at implantation site but no distinct difference was found between implantation site and pseudo-pregnant endometrium.

Co-localization of gal-3, integrin β3 and FN at the implantation site

Previous studies demonstrated that gal-3 and integrin β3 are implantation markers as they exhibit increased expression in the endometrium during implantation [15, 17]. Moreover, we have demonstrated that integrin β3 is involved in the regulation of gal-3 mediating adhesion in endometrial cells *in vitro* [13]. Here we observed that gal-3 and integrin β3 were expressed mainly in the luminal epithelium in the four groups, but gal-3 and integrin β3 expression were not observed in the blastocysts (**Figure 3**). Moreover, the intensity of gal-3 and integrin β3 expression were the highest in the implantation site but very faint in the endometrium of non-

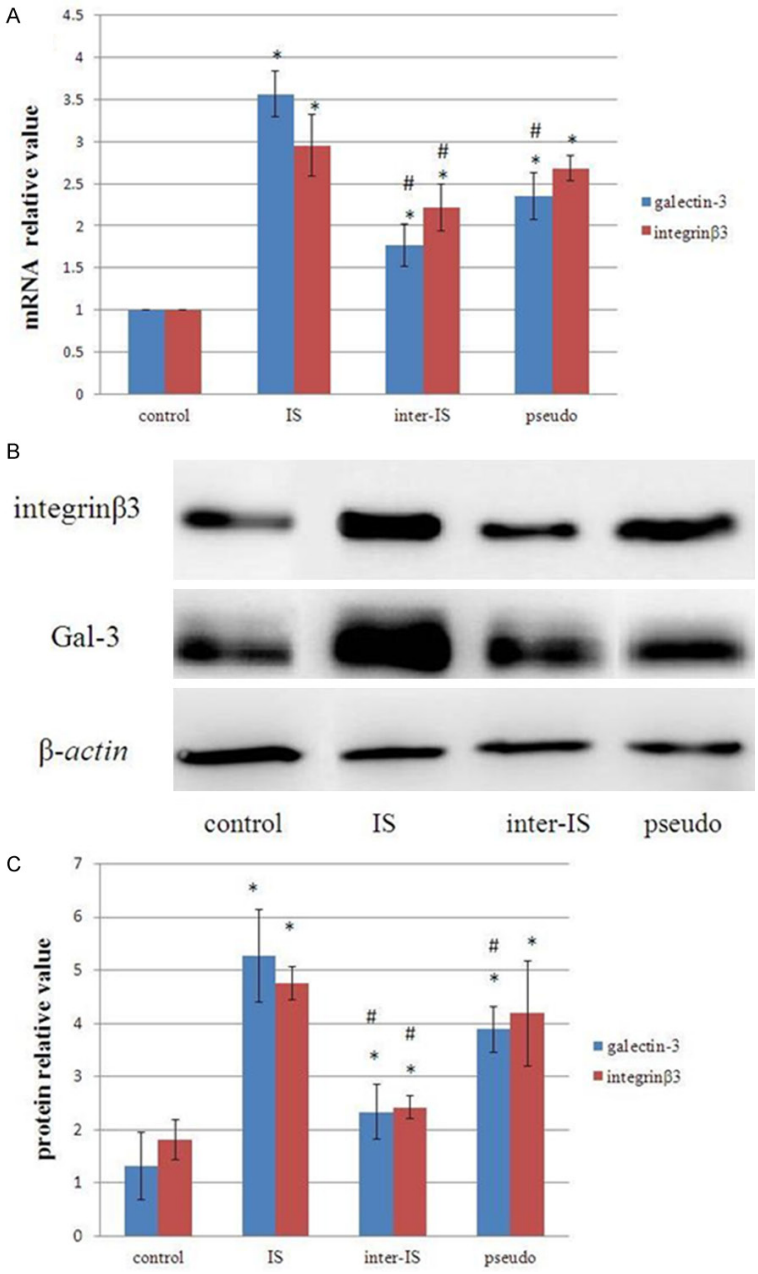

Figure 2. Expression of gal-3 and integrin β3 in the endometrium from pregnant, pseudo-pregnant and non-pregnant mice using real-time PCR (A) and Western blotting (B, C). The endometrial tissues from pregnant mice were divided into two groups: implantation site and inter-implantation site. Each sample was analyzed in triplicate. Data were analyzed using one-way ANOVA and least significant difference analysis. (*P < 0.05, compared with control; #P < 0.05, compared with implantation site. IS: implantation site; inter-IS: inter-implantation site; pseudo: pseudo-pregnancy).

pregnant mice (**Figure 3**). Interestingly, FN expression was mainly found in the stroma and the blastocyst, and there was no obvious difference in FN expression and localization among the four groups (**Figure 3**). Furthermore, we investigated the co-localization of gal-3 with integrin β3 and FN at the implantation site. As shown in **Figures 3** and **4**, gal-3 strongly colocalized with integrin β3 in the luminal epithelium at the maternal-fetal interface, especially at the implantation site; however, co-localization of gal-3 with FN was not frequently observed. These findings suggest that the co-expression of gal-3 and integrin β3 on the endometrium at the maternal-fetal interface facilitates endometrial receptivity for embryo attachment.

Discussion

Embryo implantation is a well-defined and complex process whereby the developing embryo adheres and embeds in the receptive endometrium, which is characterized by dramatic alterations in the morphology and function of the endometrial environment [18]. This process is strictly regulated by specific growth factors, cytokines, lipid mediators, adhesion molecules and transcription factors [19].

Gal-3 is differentially expressed in the window of implantation [8], with elevated expression in the mid-secretory phase of the menstrual cycle [18], which is a key period for the establishment of endometrial receptivity. Moreover, numerous studies have demonstrated that gal-3 was expressed in the decidualized endometrium [7, 20, 21]. Furthermore, Yang et al. demonstrated that the expression of gal-3 peaks during early embryo implantation (pregnant mouse on day 5) and the number of implanted embryos is substantially decreased in the mouse endometrium after selective knock down of gal-3. These findings suggest that gal-3 not only facilitates formation of the receptive endometrium

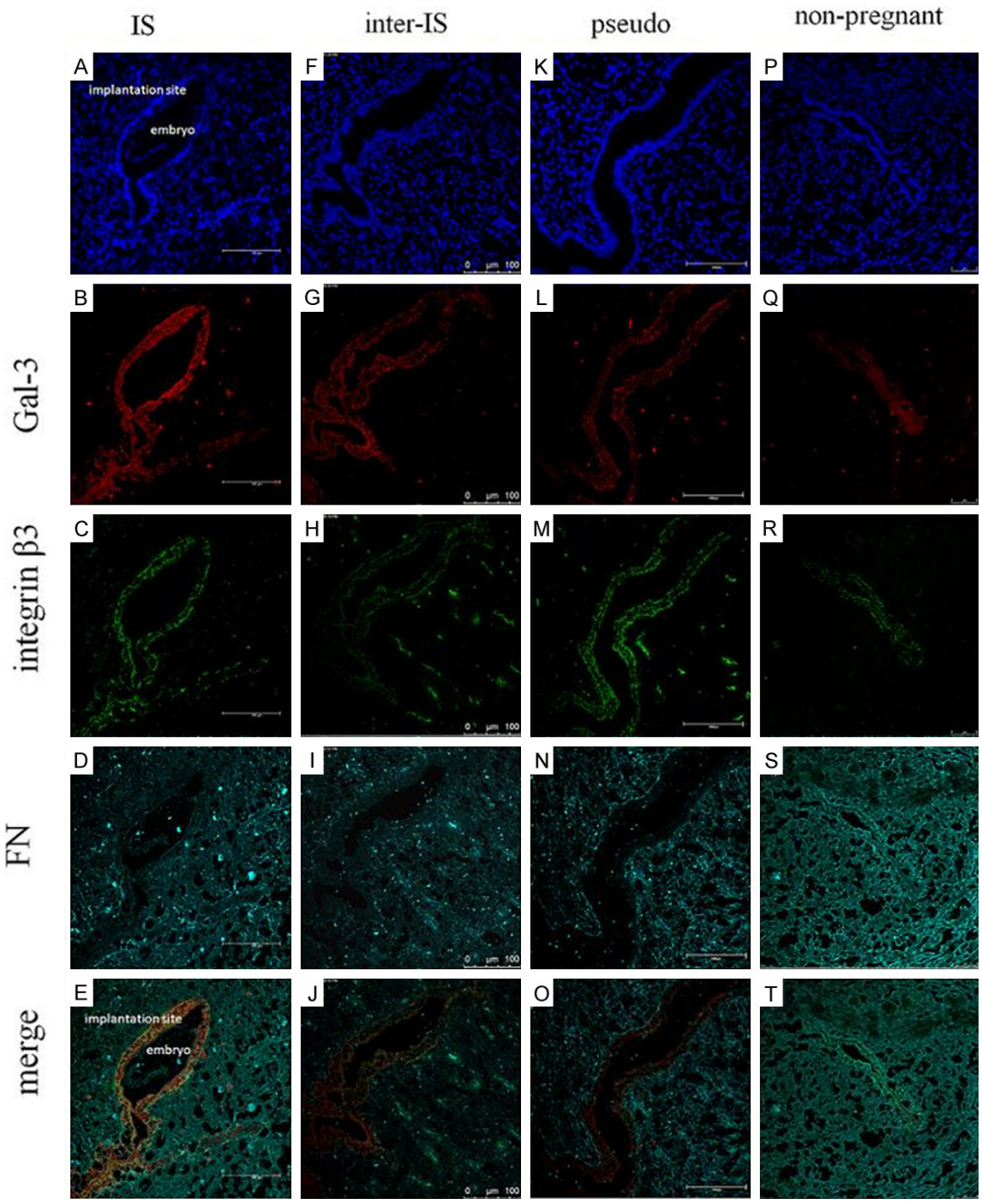

Figure 3. Immunofluorescence staining of gal-3 (red), integrin β3 (green) and FN (turquoise) in the endometrium from pregnant, pseudo-pregnant and non-pregnant mice. Nuclei were counterstained with DAPI. The immunofluorescence density in the endometrium from the implantation site (A-E) and inter-implantation site (F, G) of pregnant uteri, pseudo-pregnant uteri (H-O) and non-pregnant uteri (P-T) was compared. Experiments were performed in duplicate and repeated at least three times. Bar = 100 μm.

but also promotes maternal-embryo cross-talk. However, this morphological evidence of specific location and expression of gal-3 in the respective endometrium needs more support for our hypothesis that gal-3 involves in early embryo attachment at maternal-fetal interface.

As gal-3 ligands, integrins on the cell surface play a pivotal role in mediating cell adhesion,

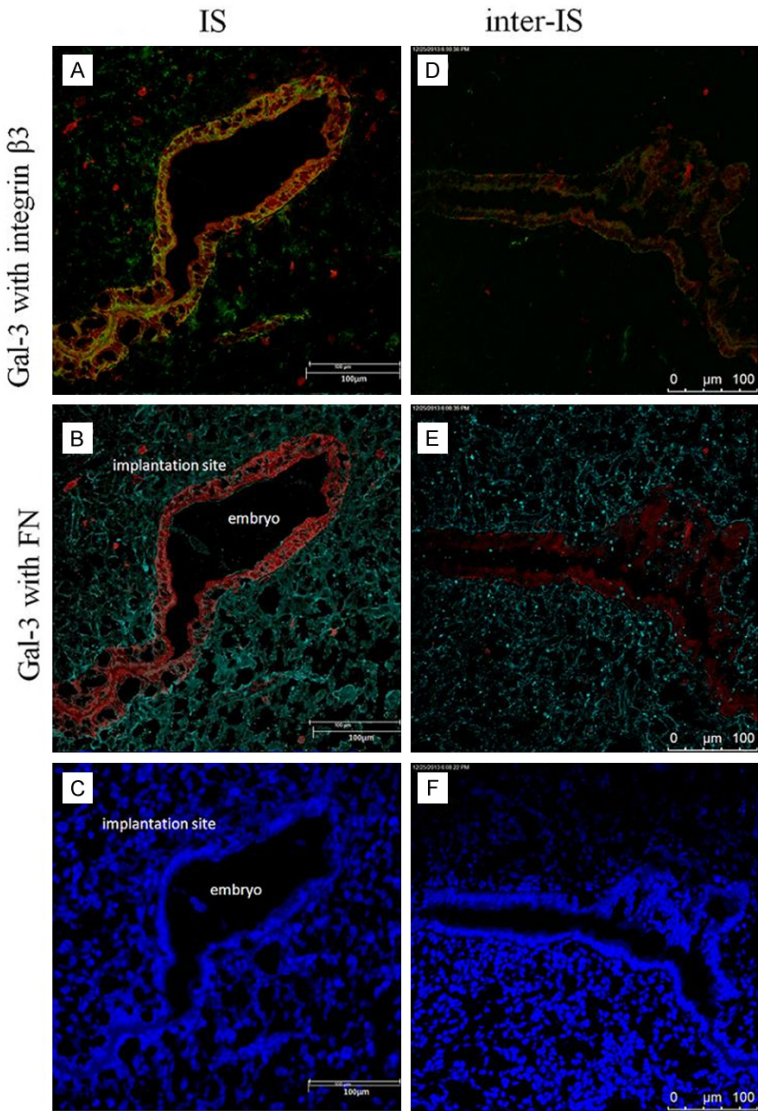

Figure 4. Representative images of co-localization of gal-3 (red) with integrin β3 (green, A, D), or FN (turquoise, B, E) in the endometrium from the implantation site and inter-implantation site of pregnant uteri. Nuclei were counterstained blue with DAPI (C, F). Experiments were performed in duplicate and repeated at least three times. Bar = 100 μm.

signal transduction and gene expression [16]. In particular, integrin αVβ3 is an epithelial marker that indicates the opening of implantation window, because it is specifically expressed in the luminal and glandular endometrial epithelium at the putative time of embryo implantation in humans [16, 22]. Although the precise mechanisms for how integrin αVβ3 functions during embryo implantation are largely unknown, it has been demonstrated that gal-3 can simultaneously change the affinity of integrins for extracellular matrix (ECM) proteins [23]. Moreover, our group demonstrated that exogenous gal-3 and integrin β1 induced endometrial cell apoptosis, but exogenous gal-3 and integrin β3 induced endometrial cell proliferation by partially competing with the apoptosis effect [24]. In terms of adhesion, the functional block of integrin β3 could result in reduced endometrial cell adhesion to FN in the presence of exogenous gal-3 [24, 25].

The premise for a successful pregnancy is embryo attaching to respective endometrium in which some molecules act as adhesive glue to help implantation. Our previous investigation suggests gal-3 expression is related to endometrium adhesion via integrin β3, a generally acknowledged adhesion molecule [24]; therefore, we assume higher expression of gal-3 in implantation window and its ligand integrin β3 play as glue to assist embryo adhere to endometrium. In this study, we provide evidence that gal-3 and integrin β3 expression are related to the endometrial state because they markedly elevated in the receptive endometrium compared with non-pregnant endometrium. Furthermore, in the receptive endometrium of mice, we demonstrated, for the first time, that gal-3 and integrin β3 expression are significantly higher at the implantation site compared to the inter-implantation site. Compared with pseudo-pregnant endometrium, the expression of gal-3 in the endometrium from the implantation site was significantly higher; on the contrary, it sees no clear difference of integrin β3 expression between implantation site and pseudo-pregnant endometrium. It indicates that embryo may be a stimulation for gal-3 spatial expression, while stronger integrin β3 expression at implantation site is not induced by embryo. These results suggest that up-regulated expression of gal-3 and its ligand integrin β3 at the implantation site may facilitate the establish-

ment of endometrial receptivity during early implantation, and the presence of an embryo may have a positive effect on gal-3 but not integrin β3 expression in the endometrium. In the immunofluorescence images, we observed abundant co-localization of gal-3 with integrin β3 but not with FN in the uterine luminal epithelium, particularly at the implantation site of the maternal-fetal interface. These findings suggest that the interaction between gal-3 and integrin β3 is conducive for embryo attachment at the implantation site of the endometrium, while FN may not be a core partner for this process in mice. These results provide solid evidence that gal-3 with its ligand integrin β3 plays a role in the establishment of a receptive endometrium for embryo implantation. However, the more factors inducing the expression of gal-3 in the endometrium require further elucidation.

In conclusion, we demonstrate that gal-3 and integrin β3 are highly expressed in the endometrium of pregnant mice, particularly at the implantation site, and gal-3 expression is highly co-localized with integrin β3 but not FN in the endometrium. Furthermore, high expression of gal-3 and integrin β3 may mediate embryo attachment at the maternal-fetal interface, although the precise mechanisms require further study.

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Disclosure of conflict of interest

None.

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