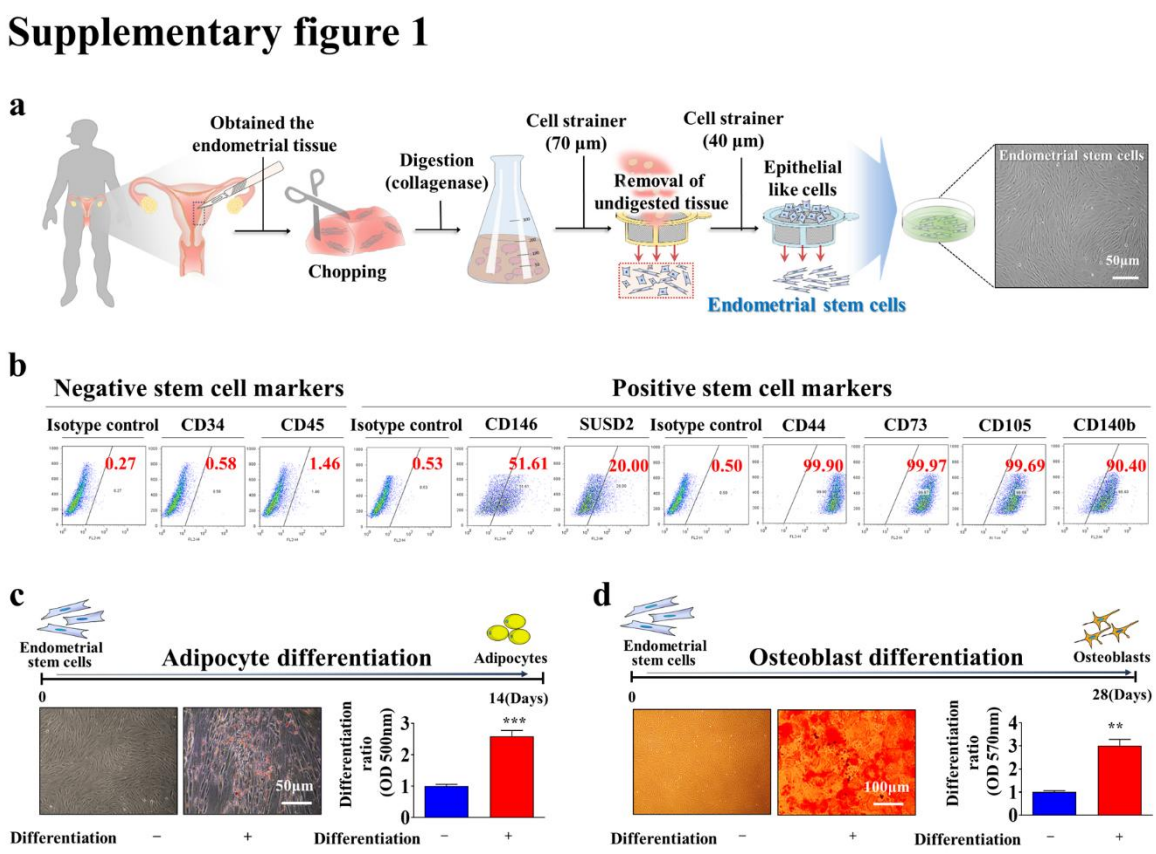
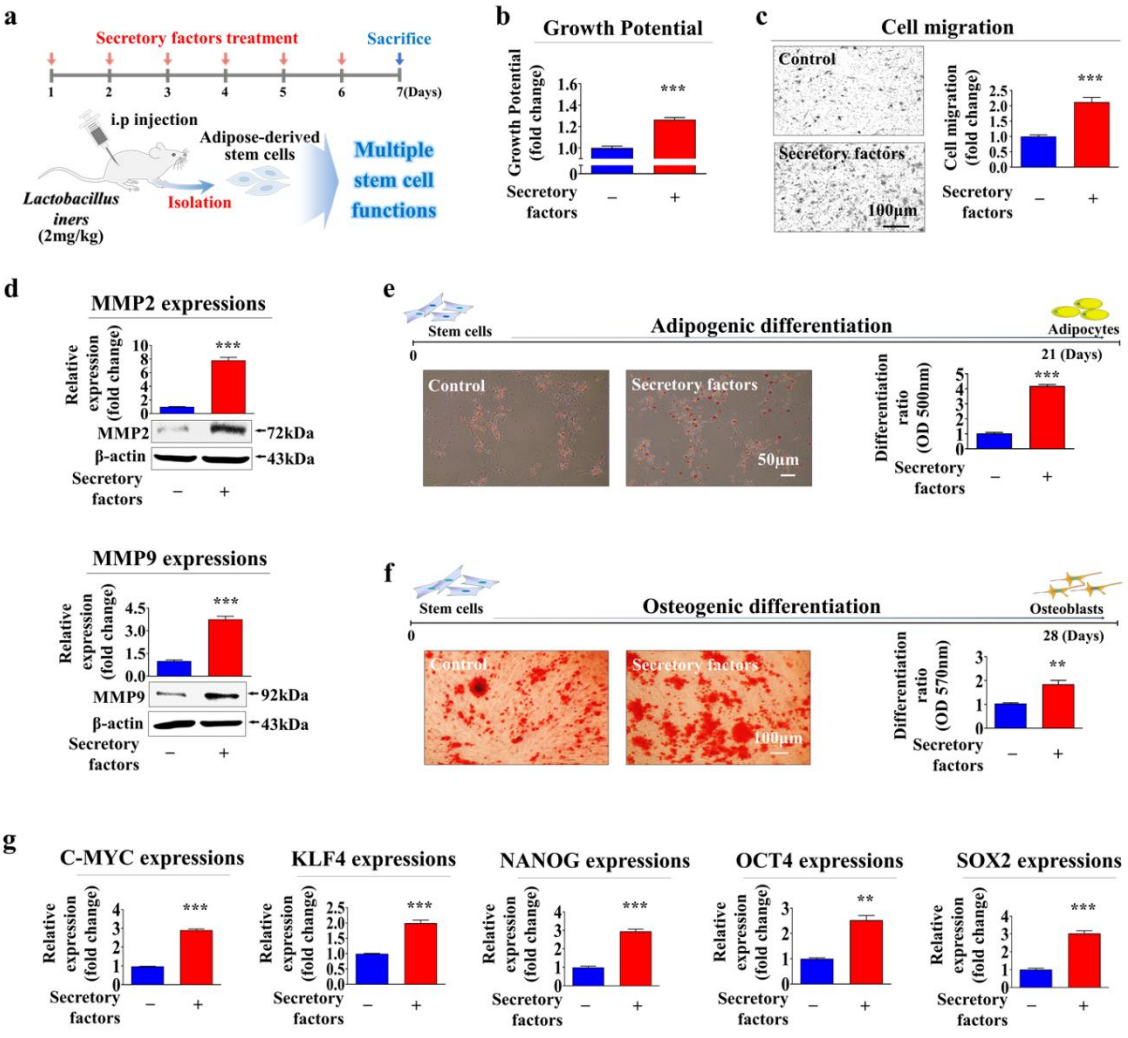
Supplementary Figures and legends



Suppl. Fig. 1. Isolation and in-depth molecular characterization of tissue-resident stem cells from human endometrial tissue. Endometrial tissue samples were meticulously dissected into small pieces and subjected to enzymatic dissociation with type I collagenase. The isolated tissue-resident stem cells were then assessed for their morphological characteristics using an inverted phase-contrast microscope **(a)**. The isolated tissue-resident stem cells were thoroughly characterized via flow cytometric analysis, utilizing a panel of antibodies specific to stem cell markers (CD44, CD73, CD105, CD140b, CD146, and SUSD2) alongside hematopoietic markers (CD34 and CD45) to ensure comprehensive profiling **(b)**. The adipogenic **(c)** and osteogenic **(d)** differentiation capacities of these stem cells were evaluated using Oil Red O and Alizarin Red S staining, respectively. Quantification of calcium deposition and lipid droplet (LD) accumulation in differentiated cells was performed by measuring the absorbance of solubilized samples at 500 and 570 nm, respectively. All experiments were performed in triplicates.

Data are presented as mean ± standard deviation (SD). *, $p < 0.05$; **, $p < 0.005$; and ***, $p < 0.001$ (two-sample *t*-test).

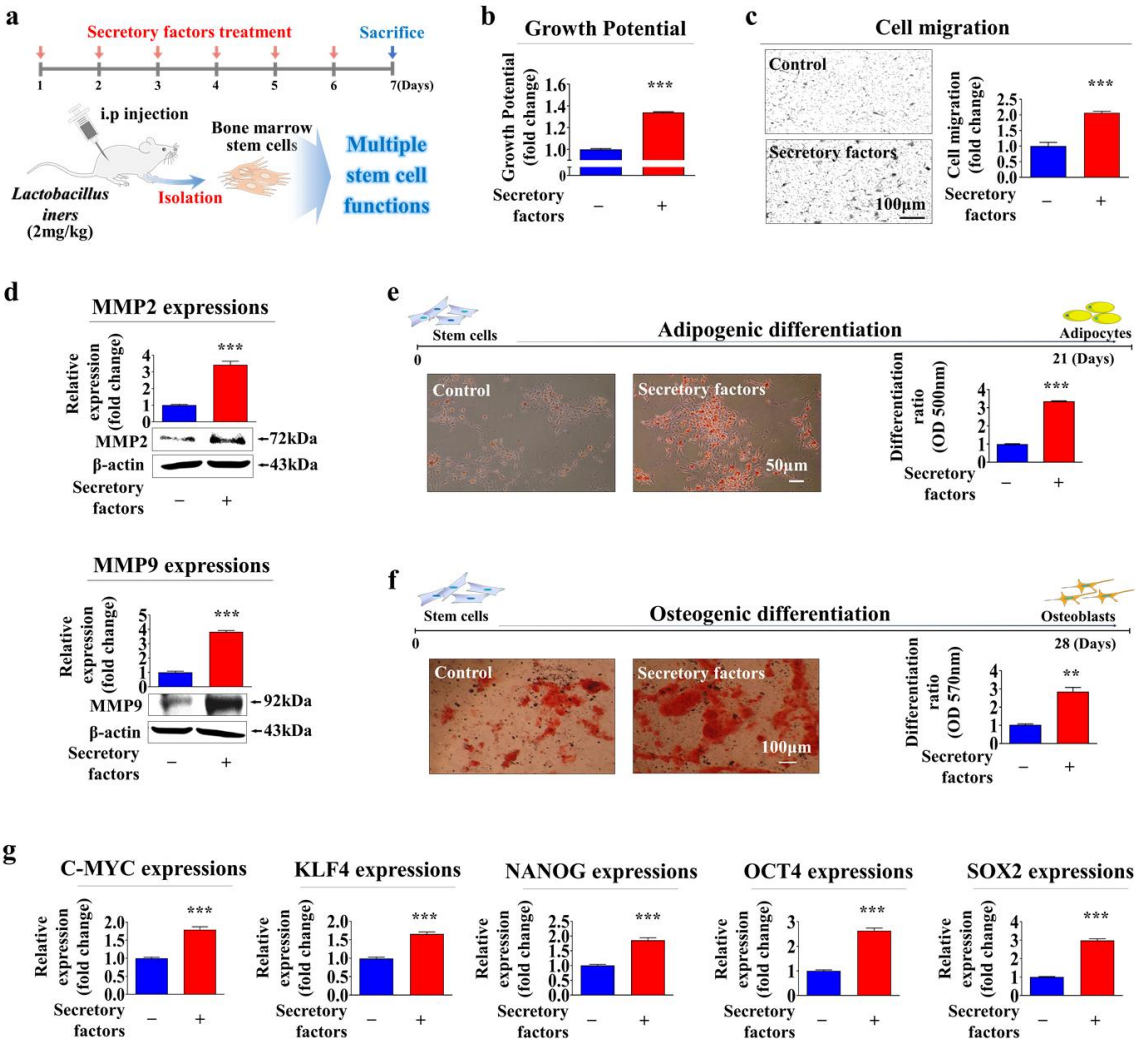
Supplementary figure 2



Suppl. Fig. 2. Influence of vaginal microbiota-derived secretory factor exposure on various tissue regeneration-associated functions of adipose tissue-derived stem cells *in vivo*. A schematic representation of the overall experimental design is outlined in the 'Materials and Methods' section **(a)**. Mice were administered consecutive intravenous injections of *Lactobacillus iners*-derived secretory factors (20 mg/kg) over the course of 1 week. Adipose tissue-derived stem cells were subsequently extracted from adipose tissue using a collagenase-based primary culture technique. Following isolation, mouse adipose tissue-derived stem cells were cultured *in vitro* with *L. iners*-derived secretory factors (10 μL/mL) to effectively recapitulate the *in vivo* microbiota-stem cell crosstalk. Next, the impact of consecutive exposure to *L. iners*-derived secretory factors on the self-renewal ability of adipose tissue-

derived stem cells *in vivo* was evaluated using an MTT assay **(b)**. The enhancement of adipose tissue-derived stem cell migratory potential following repeated *in vivo* exposure to *L. iners*-derived secretory factors was evaluated using a Transwell assay **(c)**. Western blot analysis was performed to assess the protein expression levels of key positive regulators of cell migration (MMP-2 and MMP-9) following repeated *in vivo* exposure to *L. iners*-derived secretory factors **(d)**. After repeated exposure to *L. iners*-derived secretory factors, the multilineage differentiation potential of adipose tissue-derived stem cells into adipocytes **(e)** and osteoblasts **(f)** was evaluated *in vivo* by Oil Red O and Alizarin Red S staining, respectively. The enhancing effects of repeated *L. iners*-derived secretory factors on the *in vivo* mRNA expression of key pluripotency-associated genes (*c-MYC*, *KLF4*, *NANOG*, *OCT4*, and *SOX2*) were evaluated using real-time PCR **(g)**. β-actin was used as the internal control. Mouse *HPRT* was used as the housekeeping gene for real-time PCR analysis. All experiments were performed in triplicate. Data are presented as mean ± standard deviation (SD). *, $p < 0.05$; **, $p < 0.005$; and ***, $p < 0.001$ (two-sample *t*-test).

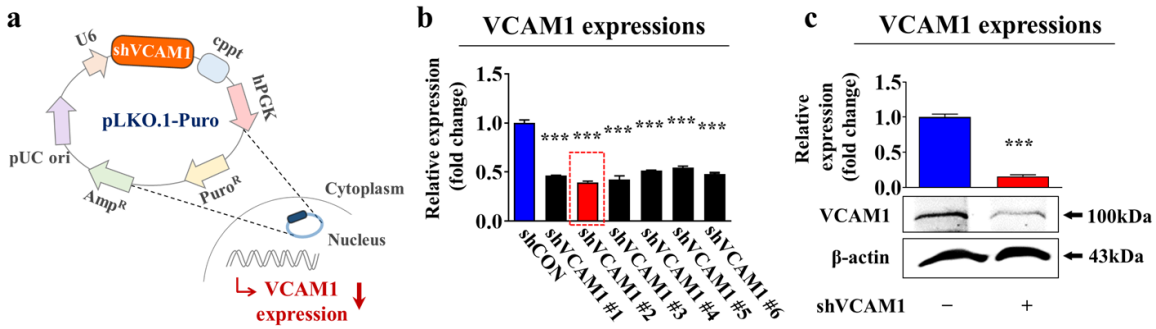
Supplementary figure 3



Suppl. Fig. 3. Influence of vaginal microbiota-derived secretory factor exposure on various tissue regeneration-associated functions of bone marrow-derived stem cells *in vivo*. A schematic representation of the overall experimental design is outlined in the 'Materials and Methods' section **(a)**. Mice were administered consecutive intravenous injections of *Lactobacillus iners*-derived secretory factors (20 mg/kg) over the course of 1 week. Following isolation, mouse bone marrow tissue-derived stem cells were cultured *in vitro* with *L. iners*-derived secretory factors (10 μL/mL) to effectively recapitulate the *in vivo* microbiota-stem cell crosstalk. Next, the impact of consecutive exposures to *L. iners*-derived secretory factors on the self-renewal ability of bone marrow-derived stem cells *in vivo* was evaluated using the MTT assay **(b)**. The enhancement of bone marrow-derived stem cell migratory

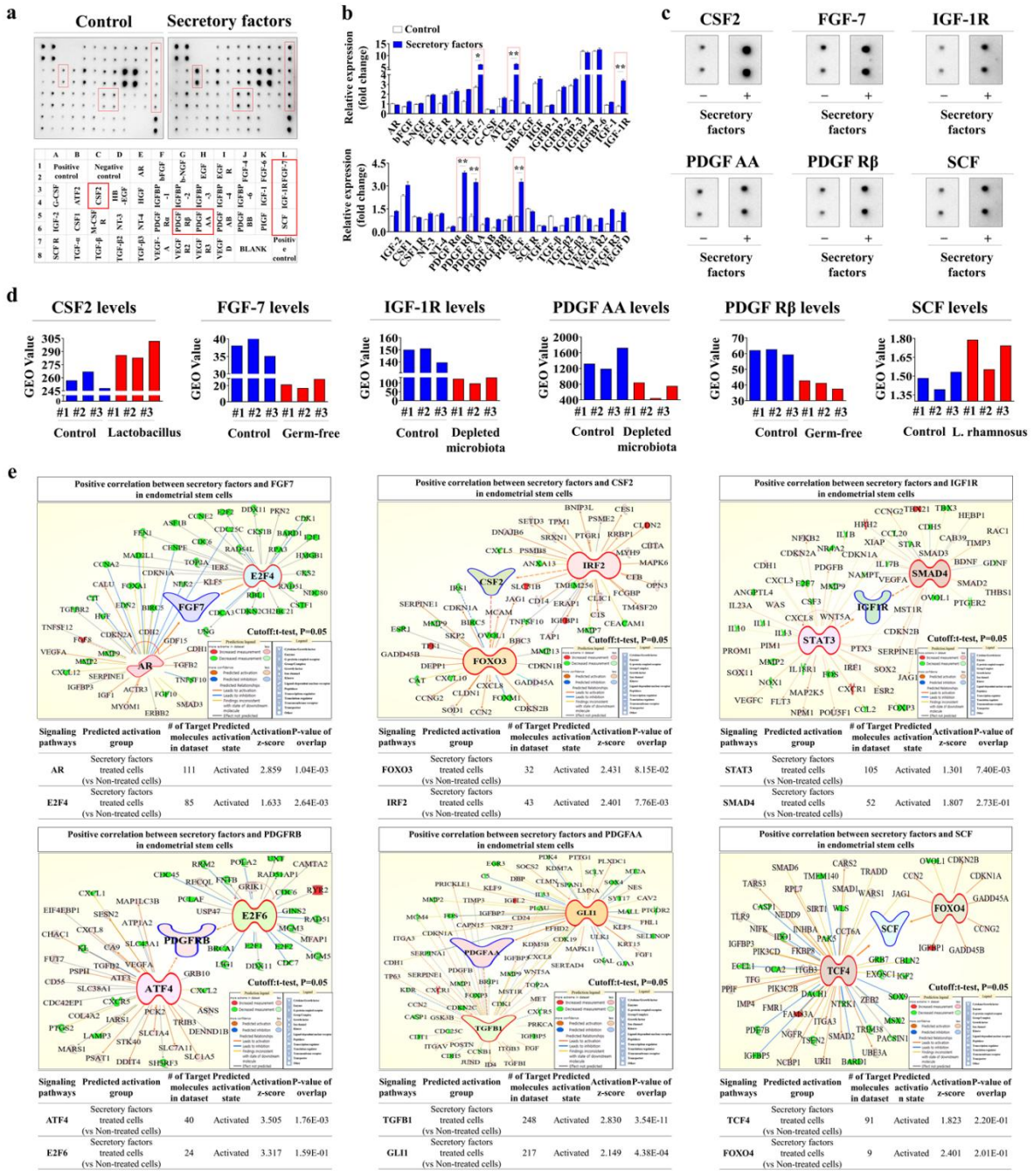
potential following repeated *in vivo* exposure to *L. iners*-derived secretory factors was evaluated using a Transwell assay **(c)**. Western blot analysis was performed to assess the protein expression levels of key positive regulators of cell migration (MMP-2 and MMP-9) following repeated *in vivo* exposure to *L. iners*-derived secretory factors **(d)**. After repeated exposure to *L. iners*-derived secretory factors, the multilineage differentiation potential of stem cells into adipocytes **(e)** and osteoblasts **(f)** was evaluated *in vivo* using Oil Red O and Alizarin Red S staining, respectively. The enhancing effects of repeated *L. iners*-derived secretory factors on the *in vivo* mRNA expression of key pluripotency-associated genes (*c-MYC*, *KLF4*, *NANOG*, *OCT4*, and *SOX2*) were evaluated using real-time PCR **(g)**. β-actin was used as the internal control. Mouse *HPRT* was used as the housekeeping gene for real-time PCR analysis. All experiments were performed in triplicate. Data are presented as mean ± standard deviation (SD). *, $p < 0.05$; **, $p < 0.005$; and ***, $p < 0.001$ (two-sample *t*-test).

Supplementary figure 4



Suppl. Fig. 4. Assessment of the efficiency of distinct shRNA constructs specifically engineered for selective VCAM1 knockdown. Endometrial stem cells were transfected with a panel of shRNA constructs (#1, #2, #3, #4, or #5) specifically targeting VCAM1, along with a non-targeting shRNA control to account for potential off-target effects **(a)**. Among the VCAM1-targeting shRNA constructs, shRNA#2—hereafter referred to as VCAM1 shRNA—exhibited the most potent knockdown efficiency. The extent of VCAM1 suppression was evaluated at the mRNA level using real-time PCR **(b)** and at the protein level using western blot analysis **(c)**. β-actin was used as an internal control. *PPIA* was used as the housekeeping gene for real-time PCR analysis. All experiments were performed in triplicate. Data are presented as mean ± standard deviation (SD). *, $p < 0.05$; **, $p < 0.005$; and ***, $p < 0.001$ (two-sample *t*-test).

Supplementary figure 5



Signaling pathways	Predicted activation group	# of Target molecules in dataset	Predicted activation state	Activation z-score	P-value of overlap
AR	Secretory factors treated cells (vs Non-treated cells)	111	Activated	2.859	1.04E-03
E2F4	Secretory factors treated cells (vs Non-treated cells)	85	Activated	1.633	2.64E-03
FOXO3	Secretory factors treated cells (vs Non-treated cells)	32	Activated	2.431	8.15E-02
IRF2	Secretory factors treated cells (vs Non-treated cells)	43	Activated	2.401	7.76E-03
STAT3	Secretory factors treated cells (vs Non-treated cells)	105	Activated	1.301	7.40E-03
SMAD4	Secretory factors treated cells (vs Non-treated cells)	52	Activated	1.807	2.73E-01
ATF4	Secretory factors treated cells (vs Non-treated cells)	40	Activated	3.505	1.76E-03
E2F6	Secretory factors treated cells (vs Non-treated cells)	24	Activated	3.317	1.59E-01
TGFB1	Secretory factors treated cells (vs Non-treated cells)	248	Activated	2.830	3.54E-11
GLI1	Secretory factors treated cells (vs Non-treated cells)	217	Activated	2.149	4.38E-04
TCF4	Secretory factors treated cells (vs Non-treated cells)	91	Activated	1.823	2.20E-01
FOXO4	Secretory factors treated cells (vs Non-treated cells)	9	Activated	2.401	2.01E-01

Suppl. Fig. 5. Exposure to vaginal microbiota-derived secretory factors stimulates the release of multiple growth factors and cytokines, which play a crucial role in facilitating stem cell-microbiota crosstalk. A human growth factor antibody array was conducted to analyze protein samples derived from *Lactobacillus iners*-derived secretory factor-treated and untreated conditions. The membrane was arrayed with antibodies targeting 40 distinct proteins. Treatment with *L. iners*-derived

secretory factors resulted in a marked upregulation of six key growth factors: colony stimulating factor 2 (CSF2), insulin-like growth factor-1 receptor (IGF-1R), keratinocyte growth factor (FGF-7), platelet-derived growth factor-AA (PDGF-AA), platelet-derived growth factor receptor β (PDGFRβ), and stem cell factor (SCF) **(a–c)**. To further investigate the associations between the six upregulated growth factors and various stem cell physiological states, an analysis of the GEO database was conducted **(d)**. To investigate whether the activation of these six protein factors-associated signaling pathways is positively linked to exposure to *L. iners*-derived secretory factors, we conducted an extensive analysis of gene expression profiles and their corresponding signaling networks using IPA. This analysis aimed to determine the activation status (active, inactive, or intermediate) of signaling molecules and transcription factors associated with Akt signaling pathway **(E)**. All experiments were performed in triplicates. Data are presented as mean ± standard deviation (SD). *, $p < 0.05$; **, $p < 0.005$; and ***, $p < 0.001$ (two-sample *t*-test).