The regulatory roles of human endometrial gland secretions at the fetal–maternal interface

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Introduction

The success of pregnancy depends on a well-established fetal-maternal interface, which mainly consisting of endometrial stromal/epithelial cells, immune cells, trophoblasts and endothelial cells. Rather than being a barrier, it serves as a region for cross-talk between the maternal and fetal cells to modulate the maternal immune system and placental development. Molecular dysregulation at the maternal-fetal interface is associated with pregnancy complications such as implantation failure and recurrent miscarriage. The endometrial gland, which is composed of glandular epithelial cells, is essential for survival/development of the conceptus by secreting and transporting various paracrine factors. This study hypothesize that the soluble factors derived from endometrial epithelial gland regulates the decidual macrophage polarization and stromal cell functions, which in turn contributes to immune tolerance and implantation during pregnancy.

Material and Method

A long-term human endometrium gland organoid culturing system was established by using endometrial tissue from women who consented to undergo an endometrial biopsy. The derived organoids were treated by sex hormones estrogen (E2), progesterone (P4), and human chorionic gonadotropin (hCG) to mimic the estrous cycle and early pregnancy environment. The effect of the organoid secretome on monocytes differentiation and stromal cell decidualization were determined. Human monocytes were isolated from female blood by immunomagnetic separation and were differentiated into macrophage using macrophage colony-stimulating factor (M-CSF; 50 ng/ml). Their phenotypes and phagocytic activity were analyzed by standard methods. The decidualization of stromal cell line (t-HESC) was determined by the expression of known decidualization markers after hormones and cAMP induction.

Results

Fig.1. Established human endometrial gland organoids recapitulate molecular signature of glands in vivo

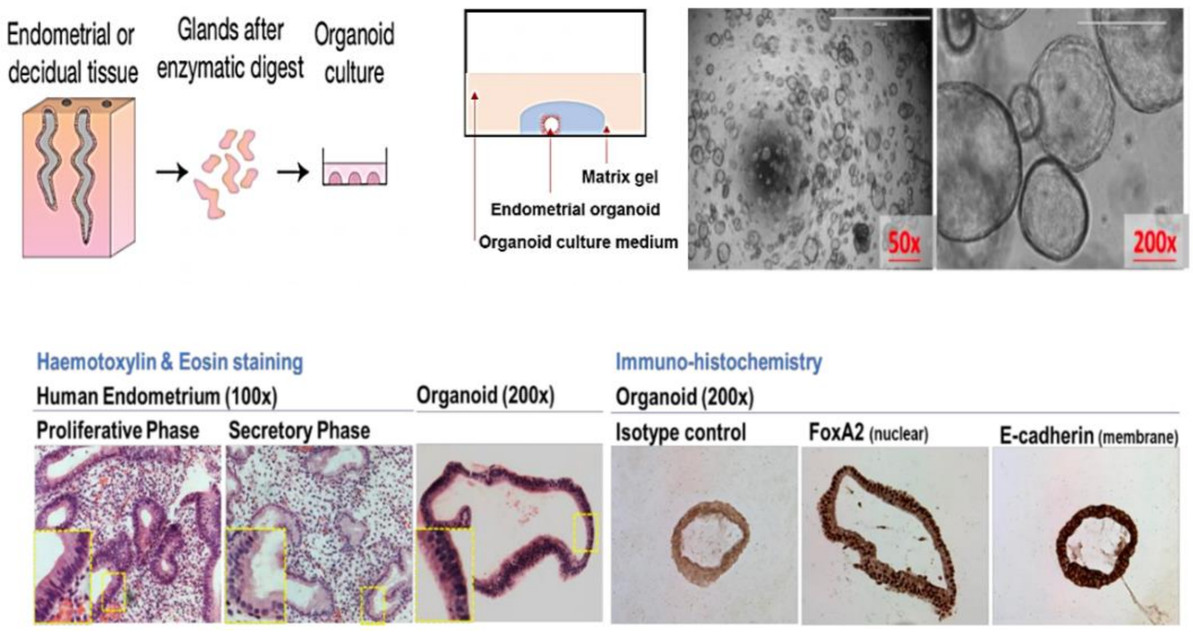
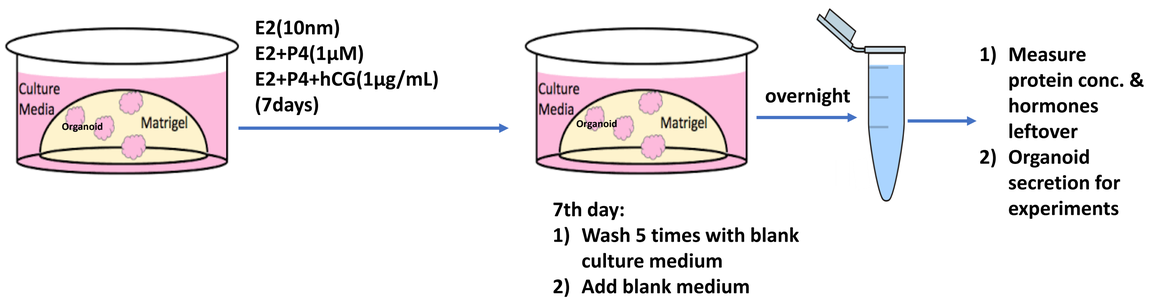
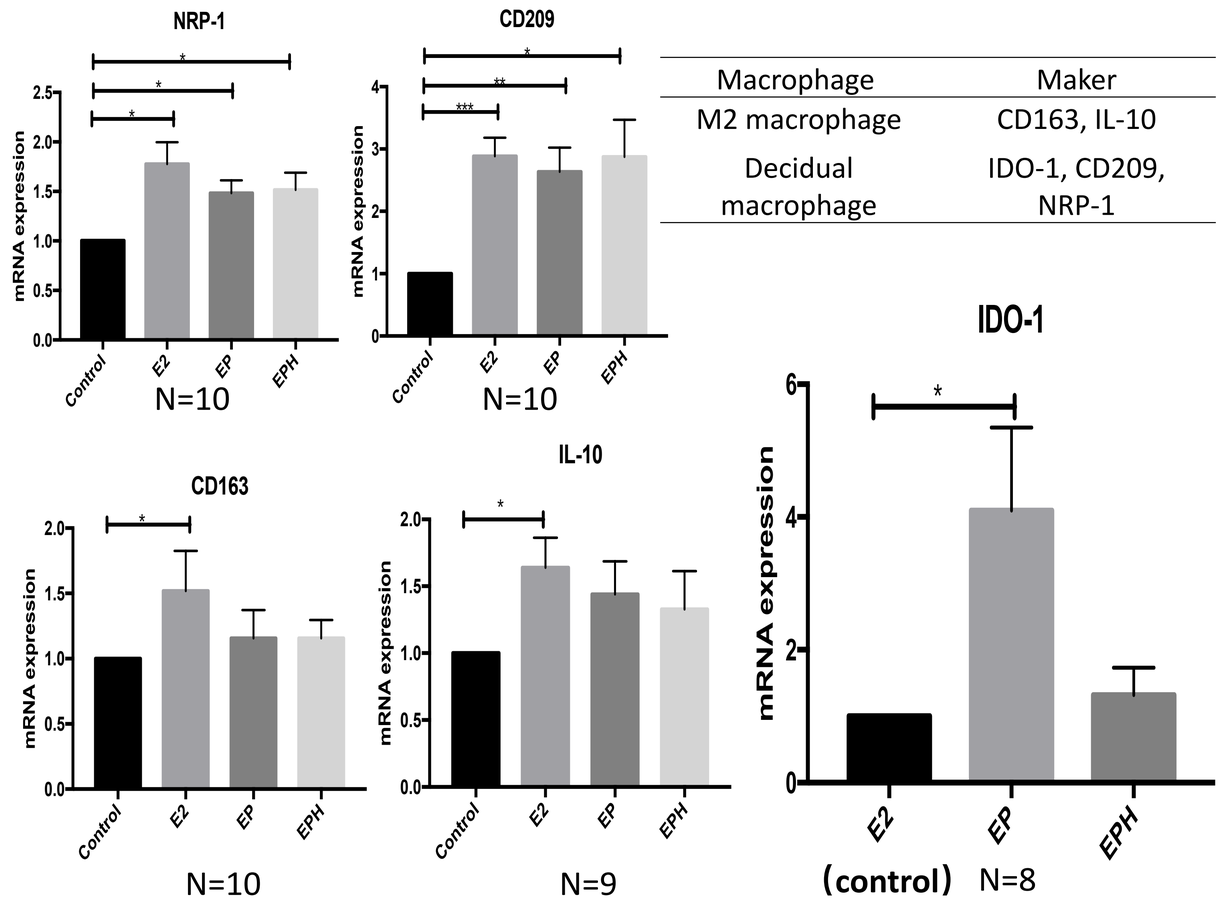


Table. 1. Organoids functionally respond to sex hormones treated by different hormones as well as total protein secretions and hormones left among the organoids with different hormone treatments. *P<0.05.



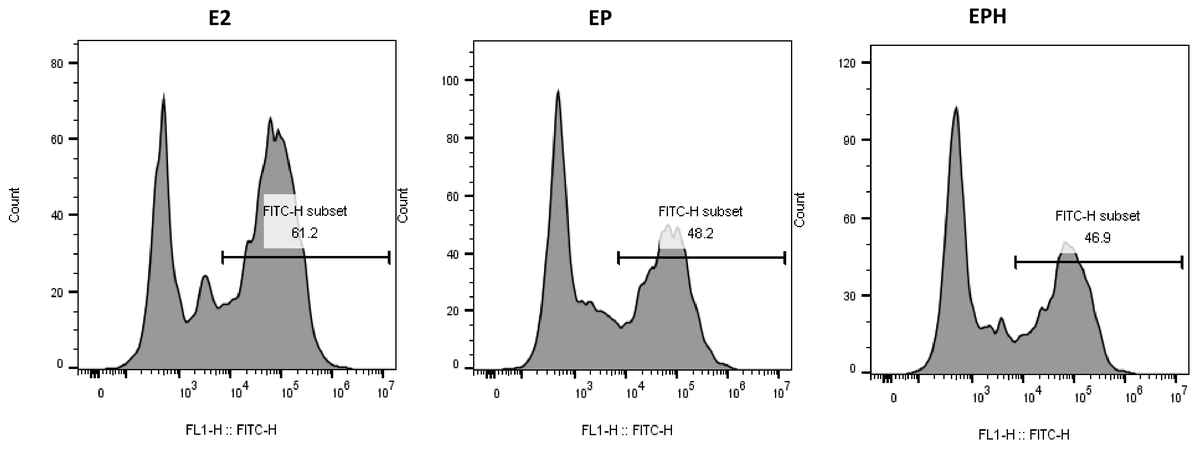
Treatment Groups	Total protein (μg/mL) (Mean± S.E.M, N=3)	Hormones concentration	GdA concentration (μg/well)
E2 (Proliferative phase)	1820.3±68.5	0.046nM	0.1
E2+P4 (Secretory phase)	1832.8±129.8	<0.0003μM	0.18
E2+P4+hCG (Early pregnancy)	1924.0±217.1	<0.000006μg/mL	0.30

Fig.5 The effect of endometrial gland secretion on the mRNA expression of decidual macrophage markers on the differentiated macrophages. Bars show the Mean ± S.E.M. with *P<0.05, **P< 0.01 and ***P<0.001 .



Macrophage	Maker
M2 macrophage	CD163, IL-10
Decidual macrophage	IDO-1, CD209, NRP-1

Fig.6 The effect of endometrial gland secretion on macrophage phagocytosis. Bars show the Mean ± S.E.M. with *P<0.05, N=4.



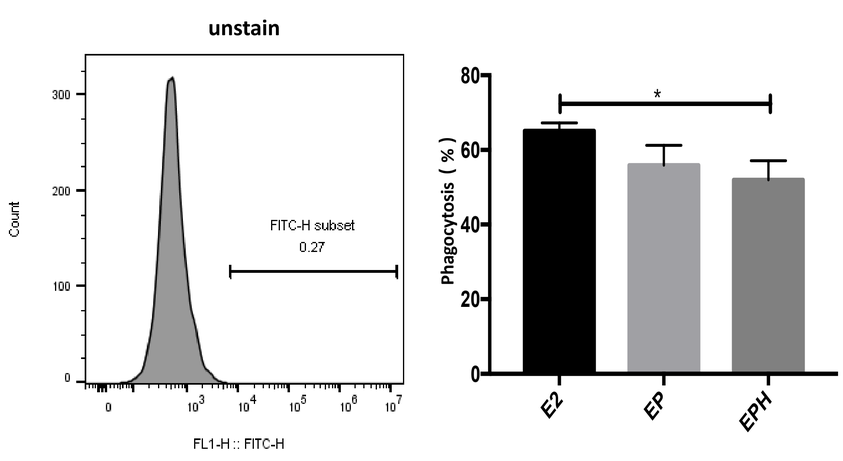
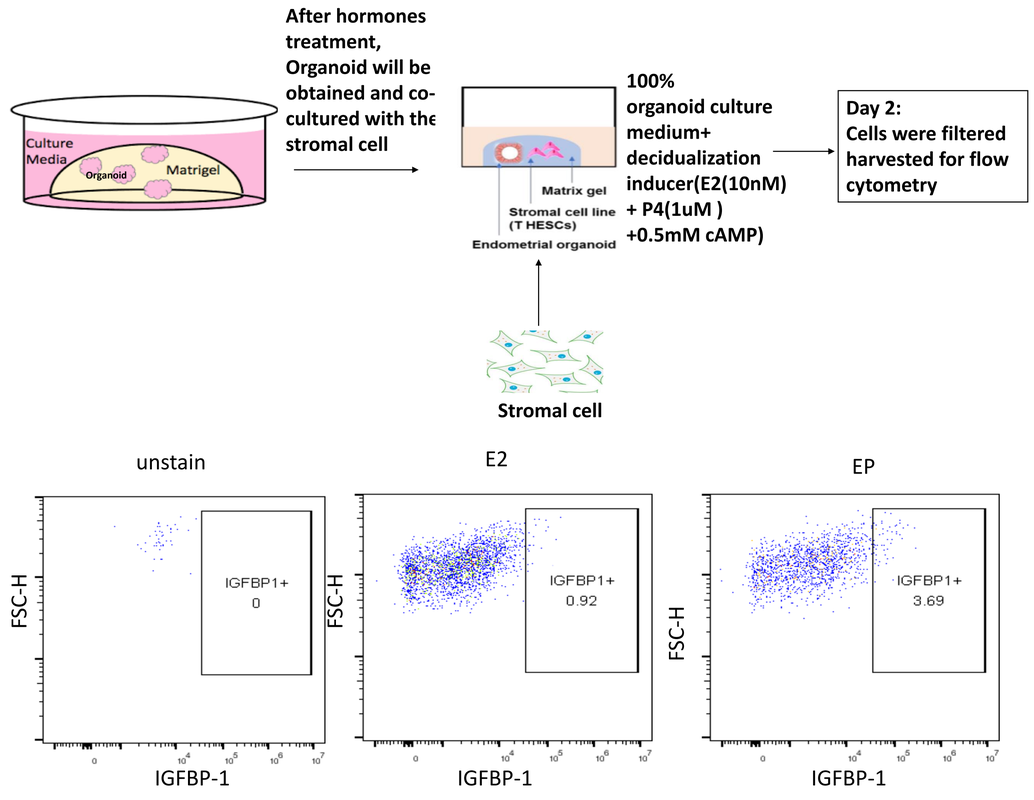


Fig.7 The effect of hormones treated organoid together with decidualization inducer on stromal cell line (t-HESC) decidualization in the co-culture model. Preliminary data (N=1)



Conclusion

By using a human glandular organoid model, our results showed that endometrial gland secretome can regulate the decidual macrophage differentiation/functions and stromal cell decidualization. Hormonal treatments modulate the secretome of organoids and their actions on endometrial cells.

Acknowledgement

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