CSF1+ secretory epithelial cells induce excessive trophoblast invasion in tubal pregnancy rupture

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Abstract (300 word limit)

Statement of the Problem: Tubal ectopic pregnancy (TEP) occurs when an embryo aberrantly implants in the fallopian tube, leading to abortive or ruptured tubal ectopic pregnancy (AEP or REP). Poor outcomes of REP include maternal infertility or mortality. Histopathology studies have demonstrated that tubal rupture is positively correlated with the depth of extravillous trophoblasts (EVT) invasion. However, after implantation, the cellular interactions within the fallopian tube that regulate EVT functions and the mechanisms leading to different pregnancy outcomes are still unclear. Methodology & Theoretical Orientation: All the maternal-fetal interface samples from IP (n=14), AEP (n=54) or REP (n=59) at gestational weeks 6-8 were collected by surgeries for histological and immunological analyses, scRNA-seq, Flow cytometry staining, real-time PCR analyses, wound closure assays, transwell assay and villous explant experiments. Findings: In REP, extravillous trophoblast cells (EVTs) form a dominant cell population, displaying aggressive invasion and proliferation, with robust differentiation into three subsets. Compared with AEP, REP has FTSECs with more abundant and higher CSF1 expression. Cell communication analysis implied that CSF1+ FTSECs can interact with EVTs and macrophages. Exogenous CSF1 could bind with CSF1R on EVTs stably overexpressing MMP2 promotes EVT proliferation, invasion, and survival *in vitro*, while exposure to GW2580 (a CSF1R antagonist) blocked CSF1-induced migration and invasion. In addition, after inducing THP-1 monocytes to differentiate into macrophages, culturing these macrophages in a medium containing purified CSF1 resulted in their polarization towards a *CD206+CD80-* Macro2-like phenotype. These cumulative results revealed that CSF1 secretion by FTSECs promotes EVT invasion and induces macrophage polarization to the macro2 response through interactions with CSF1R. Conclusion & Significance: These results provide a mechanistic context and cellular milieu leading to tubal rupture, facilitating further study and development of therapeutics for REP in early pregnancy.

Image

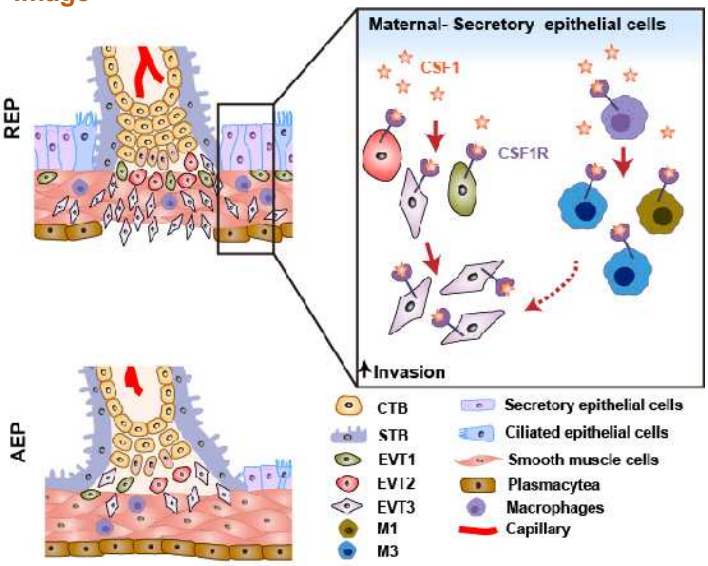


Diagram of the main receptors and ligands expressed on the secretory epithelial cells, EVTs and macrophages that are involved in invasion and cellular recruitment. REP, ruptured tubal ectopic pregnancy. AEP, abortive tubal ectopic pregnancy.

Recent Publications (minimum 5)

1. Cartwright, J.E., R. Fraser, K. Leslie, A.E. Wallace, and J.L. James, Remodelling at the maternal-fetal interface: relevance to human pregnancy disorders. Reproduction, 2010. 140(6): p. 803-13
2. Vento-Tormo, R., M. Efremova, R.A. Botting, M.Y. Turco, M. Vento-Tormo, K.B. Meyer, et al., Single-cell reconstruction of the early maternal-fetal interface in humans. Nature, 2018. 563(7731): p. 347-53
3. Wu, Z.M., H. Yang, M. Li, C.C. Yeh, F. Schatz, C.J. Lockwood, et al., Pro-inflammatory cytokine-stimulated first trimester decidual cells enhance macrophage-induced apoptosis of extravillous trophoblasts. Placenta, 2012. 33(3): p. 188-94.
4. Wang, X., C.L. Lee, R.H.W. Li, M. Vijayan, Y.G. Duan, W.S.B. Yeung, et al., Alteration of the immune cell profiles in the pathophysiology of tubal ectopic pregnancy. Am J Reprod Immunol, 2019. 81(4): p. e13093
5. Ahmad, S.F., W.C. Duncan, L.L. Campbell, R.E. Beaty, M. Koscielniak, F. Collins, et al., Targeting colony stimulating factor-1 receptor signalling to treat ectopic pregnancy. Sci Rep, 2020. 10(1): p. 15638

Photograph



Biography (150 word limit)

Mrs. Zhao majors in Obstetrics and Gynecology at Shanghai Jiaotong University of Medicine and is currently a second-year Ph.D. student. Mrs. Zhao is aimed at investigating the molecular mechanisms involved in placental development, particularly in pathological pregnancy. Considering the lack of EP phenotypes in rodents and fundamental differences in placental structures between mice and humans, we established human endometrium organoids, placental organoids, and fallopian tubal organoids to investigate the pathogenesis of ectopic pregnancy.

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Notes/Comments:

We are pleased to submit our abstract entitled "**CSF1+ secretory epithelial cells induce excessive trophoblast invasion in tubal pregnancy rupture",** for consideration to be accepted as a poster**.** We are very grateful for your consideration and careful handling of our abstract, and we look forward to your reply.